```
=> fil reg; d que l6; d que l3
FILE 'REGISTRY' ENTERED AT 15:04:32 ON 19 JUN 2002
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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STRUCTURE FILE UPDATES:   17 JUN 2002  HIGHEST RN 431874-59-8
DICTIONARY FILE UPDATES:  17 JUN 2002  HIGHEST RN 431874-59-8

TSCA INFORMATION NOW CURRENT THROUGH January 7, 2002

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Crossover limits have been increased.  See HELP CROSSOVER for details.

Calculated physical property data is now available.  See HELP PROPERTIES
for more information.  See STNote 27, Searching Properties in the CAS
Registry File, for complete details:
http://www.cas.org/ONLINE/STN/STNOTES/stnotes27.pdf
```

Seq of claim 12 or claim 13

```
L6             0 SEA FILE=REGISTRY ABB=ON  YRDAIFTNRYRKVL'ABU'QLSARKLLQDI'NLE'R'
                 HAR'|YRDAIFTN'HAR'YRKVL'ABU'QLSARKLLQDI'NLE'R'HAR'/SQSP
```

Sequence of claim 11 — any amino acid (Registry file doesn't recognize the code 'NAL')

```
L3            65 SEA FILE=REGISTRY ABB=ON  [YH][R'CIT']DA[IV]T[NQSTA'ABU''AIB']
                 [R'HAR'K'ORN''CIT''NLE'YSA'AIB'][YF]R[K'ORN'][V'NLE'][L'NLE'][G
                 A'ABU''NLE'Q][QR]L[S'NLE'][A'ABU']R[K'ORN'][LA'AIB']LQDI[ML'NLE
                 ''ABU'R][RSNDA'ABU'][R'HAR']/SQSP


=> d l3 rn cn sql kwic nte 1-65; fil capl; d que l4

L3   ANSWER 1 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   309244-12-0  REGISTRY  — Use Registry # to match sequence to citation
CN   114: PN: WO0069900 SEQID: 118 unclaimed sequence (9CI)  (CA INDEX NAME)
SQL  29
```

sequence length

```
SEQ      1 YRDAIFTNRY RKVLGQLSAR KLLQDIMSR
           ========== ========== ========= (29-mer)
HITS AT:   1-29

L3   ANSWER 2 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   286850-19-9  REGISTRY
CN   L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-
     alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-
     arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-
     L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-
     L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI)
     (CA INDEX NAME)
SQL  29

SEQ      1 YRDAIFTNRY RKVLXQLSAR KLLQDIXSR
           ========== ========== =========
HITS AT:   1-29
NTE  modified (modifications unspecified)
```

type	location		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-

stereo	Arg-2	-	D

L3 ANSWER 3 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 265307-91-3 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-O-methyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-D-arginyl-L-arginyl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIRRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
stereo	Arg-2	-	D
stereo	Arg-27	-	D
stereo	Arg-29	-	D

L3 ANSWER 4 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 265307-63-9 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-O-methyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 5 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-80-6 REGISTRY
CN L-Lysinamide, N-(1-naphthalenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	location		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 6 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-79-3 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-N6-(aminoiminomethyl)-L-lysyl-O-methyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN JV 1-36
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	location		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 7 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-78-2 REGISTRY
CN L-Lysinamide, N-(1H-indol-3-ylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	location		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 8 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-77-1 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-O-methyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-

aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 9 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-76-0 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-N6-(aminoiminomethyl)-L-lysyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 10 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-60-2 REGISTRY
CN L-Lysinamide, N-(1-naphthalenylacetyl)-L-histidyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 11 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-59-9 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 12 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-58-8 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-histidyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN JV 1-42
SQL 29

SEQ 1 HRDAIFTNRY RKVLXQLSAR KLLQDIXRR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 13 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-57-7 REGISTRY
CN L-Lysinamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-D-arginyl-N6-(aminoiminomethyl)- (9CI) (CA INDEX NAME)
OTHER NAMES:
CN MZ 6-55
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXRR
========== ========== =========

HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-28	-	D

L3 ANSWER 14 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-52-2 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-arginyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNRY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 15 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-49-7 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-norleucyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNXY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Nle-9	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 16 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-46-4 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-

glutaminyl-L-leucyl-L-norleucyl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLXAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-18	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 17 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-30-6 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-L-norleucine-27-L-norleucine-29-D-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Nle-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 18 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 221377-28-2 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-arginyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXRLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 19 OF 65 REGISTRY COPYRIGHT 2002 ACS

RN 221377-16-8 REGISTRY
CN D-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-norleucyl-L-norleucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKXXXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Nle-13	-	-
uncommon	Nle-14	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 20 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 216368-91-1 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 2-[N5-(aminocarbonyl)-L-ornithine]-6-(4-chloro-L-phenylalanine)-15-[(2S)-2-aminobutanoic acid]-27-L-norleucine- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YXDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
uncommon	Cit-2	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 21 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-84-2 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-iodo-L-phenylalanine)-10-(O-methyl-L-tyrosine)-15-[(2S)-2-aminobutanoic acid]-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 22 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-83-1 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-chloro-L-phenylalanine)-10-(O-methyl-L-tyrosine)-15-[(2S)-2-aminobutanoic acid]-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 23 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-82-0 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-iodo-L-phenylalanine)-15-[(2S)-2-aminobutanoic acid]-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 24 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-81-9 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-fluoro-L-phenylalanine)-15-[(2S)-2-aminobutanoic acid]-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 25 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-80-8 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-[(2S)-2-aminobutanoic acid]-27-L-

norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 26 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204866-79-5 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-L-asparaginyl-L-seryl-4-chloro-L-phenylalanyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSF RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 27 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204767-61-3 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-2-methylalanyl-2-methylalanyl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXXY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Aib-8	-	-
uncommon	Aib-9	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	Tyr-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 28 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 204767-60-2 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-2-methylalanyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-(2S)-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Aib-8	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	Tyr-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 29 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 198404-60-3 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-[O-methyl-N-(phenylacetyl)-L-tyrosine]-2-D-arginine-15-L-alanine-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Nle-27	-	-
modification	Tyr-1	-	undetermined modification
modification	Tyr-1	-	methyl<Me>

L3 ANSWER 30 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190975-94-1 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-3-(2-naphthalenyl)-L-alanyl-L-threonyl-(2S)-2-aminobutanoyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-(2S)-2-aminobutanoyl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIATXSY RKVLAQLSAR KLLQDIXXR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-8	-	-

uncommon	Nle-27	-	-
uncommon	Abu-28	-	-
stereo	Arg-2	-	D

L3 ANSWER 31 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190975-92-9 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-[O-methyl-N-(phenylacetyl)-L-tyrosine]-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-L-alanine-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	location		description
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 32 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190791-08-3 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-(2S)-2-aminobutanoyl-L-seryl-L-tyrosyl-L-arginyl-D-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLAQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	location		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-8	-	-
uncommon	Nle-27	-	-
modification	Tyr-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 33 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190791-07-2 REGISTRY
CN L-Argininamide, N-acetyl-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-(2S)-2-aminobutanoyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-(2S)-2-aminobutanoyl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLAQLSAR KLLQDIXXR
========== ========== =========
HITS AT: 1-29
NTE modified

type	location		description

terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-8	-	-
uncommon	Nle-27	-	-
uncommon	Abu-28	-	-
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 34 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190791-06-1 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(phenylacetyl)-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-L-alanine-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	location		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Nle-27	-	-
modification	Tyr-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 35 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190783-59-6 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-(2S)-2-aminobutanoyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-(2S)-2-aminobutanoyl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLAQLSAR KLLQDIXXR
========== ========== =========
HITS AT: 1-29
NTE modified

type	location		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-8	-	-
uncommon	Nle-27	-	-
uncommon	Abu-28	-	-
modification	Tyr-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 36 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 190783-58-5 REGISTRY
CN L-Argininamide, N-(phenylacetyl)-L-tyrosyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-4-chloro-L-phenylalanyl-L-threonyl-(2S)-2-aminobutanoyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLAQLSAR KLLQDIXSR

```
          ========== ========== =========
HITS AT:    1-29
NTE  modified
-----------------------------------------------------------------------
 type             ------ location ------          description
-----------------------------------------------------------------------
terminal mod.     Arg-29           -          C-terminal amide
uncommon          Abu-8            -          -
uncommon          Nle-27           -          -
modification      Tyr-1            -          undetermined modification
modification      Phe-6            -          chloro<Cl>
-----------------------------------------------------------------------

L3   ANSWER 37 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   171047-69-1  REGISTRY
CN   1-29-Somatoliberin (human pancreatic islet), N-(2-methyl-1-oxopropyl)-2-D-
     arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic
     acid)-19-(L-2-aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI)
     (CA INDEX NAME)
SQL  29

SEQ      1 YRDAIFTNSY RKVLXQLSXR KLLQDIXSR
           ========== ========== =========
HITS AT:    1-29
NTE  modified
-----------------------------------------------------------------------
 type             ------ location ------          description
-----------------------------------------------------------------------
terminal mod.     Arg-29           -          C-terminal amide
uncommon          Abu-15           -          -
uncommon          Abu-19           -          -
uncommon          Nle-27           -          -
modification      Tyr-1            -          2-methyl-1-oxopropyl<i-BuO>
modification      Phe-6            -          chloro<Cl>
-----------------------------------------------------------------------

L3   ANSWER 38 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   171047-67-9  REGISTRY
CN   1-29-Somatoliberin (human pancreatic islet), N-(2-methyl-1-oxopropyl)-2-D-
     arginine-6-(4-chloro-L-phenylalanine)-8-(2-methylalanine)-15-(L-2-
     aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI)  (CA INDEX
     NAME)
SQL  29

SEQ      1 YRDAIFTXSY RKVLXQLSAR KLLQDIXSR
           ========== ========== =========
HITS AT:    1-29
NTE  modified
-----------------------------------------------------------------------
 type             ------ location ------          description
-----------------------------------------------------------------------
terminal mod.     Arg-29           -          C-terminal amide
uncommon          Aib-8            -          -
uncommon          Abu-15           -          -
uncommon          Nle-27           -          -
modification      Tyr-1            -          2-methyl-1-oxopropyl<i-BuO>
modification      Phe-6            -          chloro<Cl>
-----------------------------------------------------------------------

L3   ANSWER 39 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   171047-66-8  REGISTRY
CN   1-29-Somatoliberin (human pancreatic islet), N-(2-methyl-1-oxopropyl)-2-D-
     arginine-8-(2-methylalanine)-15-(L-2-aminobutanoic acid)-27-L-norleucine-
```

29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTXSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Aib-8	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	Tyr-1	-	2-methyl-1-oxopropyl<i-BuO>

L3 ANSWER 40 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 171047-64-6 REGISTRY
CN L-Argininamide, N-(iodoacetyl)-L-histidyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbonyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIXTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Aaa-6	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 41 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 171047-63-5 REGISTRY
CN L-Argininamide, N-(2-methyl-1-oxopropyl)-L-histidyl-D-arginyl-L-.alpha.-aspartyl-L-alanyl-L-isoleucyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carbonyl-L-threonyl-L-asparaginyl-L-seryl-L-tyrosyl-L-arginyl-L-lysyl-L-valyl-L-leucyl-L-2-aminobutanoyl-L-glutaminyl-L-leucyl-L-seryl-L-alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-L-isoleucyl-L-norleucyl-L-seryl- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIXTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Aaa-6	-	-
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 42 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 160499-40-1 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-(1-naphthalenylacetyl)-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 43 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 160499-35-4 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-[N-(1-naphthalenylacetyl)-L-histidine]-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified (modifications unspecified)

type	------ location ------		description
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
stereo	Arg-2	-	D

L3 ANSWER 44 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 160361-95-5 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-[N-(iodoacetyl)-L-histidine]-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	His-1	-	undetermined modification
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 45 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 160361-94-4 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-[N-(2-methyl-1-oxopropyl)-L-histidine]-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic

acid)-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	His-1	-	2-methyl-1-oxopropyl<i-BuO>
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 46 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 160361-93-3 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), 1-(N-acetyl-L-histidine)-2-D-arginine-6-(4-chloro-L-phenylalanine)-15-(L-2-aminobutanoic acid)-27-L-norleucine-29-L-argininamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 HRDAIFTNSY RKVLXQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	His-1	-	N-acetyl
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Abu-15	-	-
uncommon	Nle-27	-	-
modification	Phe-6	-	chloro<Cl>

L3 ANSWER 47 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 148298-15-1 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-L-arginine-15-L-alanine-27-L-leucine-28-L-asparagine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDILNR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 48 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 138659-26-4 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-8-L-alanine-9-L-alanine-15-L-alanine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-

L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTAAY RKVLAQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 49 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 138659-25-3 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-8-L-alanine-15-L-alanine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTASY RKVLAQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 50 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 138659-23-1 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-27-L-leucine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDILSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 51 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 127119-77-1 REGISTRY BBRC 167, 360-6
CN Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-29-D-arginine-30-L-tyrosine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 30

```
SEQ      1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRY
           ========== ========== =========
HITS AT:   1-29
NTE
----------------------------------------------------------------------
 type            ------ location ------        description
----------------------------------------------------------------------
terminal mod.    Tyr-1           -         N-acetyl
stereo           Arg-2           -         D
stereo           Arg-29          -         D
----------------------------------------------------------------------

L3   ANSWER 52 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   126883-98-5  REGISTRY
CN   Somatoliberin (human pancreatic islet), 2-D-arginine-29-D-arginine-30-de-L-
     glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic
     acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic
     acid-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-
     arginine-44-de-L-leucinamide- (9CI)  (CA INDEX NAME)
SQL  30

SEQ      1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRR
           ========== ========== =========
HITS AT:   1-29

L3   ANSWER 53 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   126883-97-4  REGISTRY
CN   L-Argininamide, L-tyrosyl-D-arginyl-D-.alpha.-aspartyl-L-alanyl-L-
     isoleucyl-L-phenylalanyl-L-threonyl-D-asparaginyl-L-seryl-D-tyrosyl-D-
     arginyl-L-lysyl-L-valyl-L-leucyl-L-alanyl-L-glutaminyl-L-leucyl-L-seryl-L-
     alanyl-L-arginyl-L-lysyl-L-leucyl-L-leucyl-L-glutaminyl-L-.alpha.-aspartyl-
     L-isoleucyl-L-methionyl-L-seryl- (9CI)  (CA INDEX NAME)
SQL  29

SEQ      1 YRDAIFTNSY RKVLAQLSAR KLLQDIMSR
           ========== ========== =========
HITS AT:   1-29
NTE  modified
----------------------------------------------------------------------
 type            ------ location ------        description
----------------------------------------------------------------------
terminal mod.    Arg-29          -         C-terminal amide
----------------------------------------------------------------------

L3   ANSWER 54 OF 65  REGISTRY  COPYRIGHT 2002 ACS
RN   121448-26-8  REGISTRY      8 BBRC
CN   Somatoliberin (human pancreatic islet), 2-D-arginine- (9CI)  (CA INDEX
     NAME)
SQL  44

SEQ      1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRQ QGESNQERGA RARL
           ========== ========== =========
HITS AT:   1-29
NTE  modified
----------------------------------------------------------------------
 type            ------ location ------        description
----------------------------------------------------------------------
terminal mod.    Leu-44          -         C-terminal amide
stereo           Arg-2           -         D
----------------------------------------------------------------------

L3   ANSWER 55 OF 65  REGISTRY  COPYRIGHT 2002 ACS
```

RN 121396-19-8 REGISTRY
CN Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-29-D-arginine-30-L-tyrosinamide-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 30

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRY
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Tyr-30	-	C-terminal amide
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 56 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121396-17-6 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-29-D-arginine-30-L-tyrosinamide-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 30

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRY
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-30	-	C-terminal amide
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 57 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121396-16-5 REGISTRY
CN Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-29-D-arginine-30-L-argininamide-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 30

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Arg-30	-	C-terminal amide
stereo	Arg-2	-	D
stereo	Arg-29	-	D

L3 ANSWER 58 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121282-58-4 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-29-D-arginine-30-L-argininamide-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 30

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSRR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-30	-	C-terminal amide

L3 ANSWER 59 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121282-57-3 REGISTRY
CN Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-8-D-asparagine-15-L-alanine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 60 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121282-56-2 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-8-D-asparagine-15-L-alanine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLAQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 61 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 121282-52-8 REGISTRY

CN Somatoliberin (human pancreatic islet), 2-L-arginine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 62 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 110781-88-9 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-27-L-norleucine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIXSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide
uncommon	Nle-27	-	-

L3 ANSWER 63 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 104670-95-3 REGISTRY
CN Somatoliberin (human pancreatic islet), 1-(N-acetyl-D-tyrosine)-2-D-arginine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 64 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 93942-95-1 REGISTRY
CN Somatoliberin (human pancreatic islet), 2-D-arginine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic

acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide- (9CI) (CA INDEX NAME)
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Arg-29	-	C-terminal amide

L3 ANSWER 65 OF 65 REGISTRY COPYRIGHT 2002 ACS
RN 93942-91-7 REGISTRY
CN 1-29-Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-29-L-argininamide- (9CI) (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN Somatoliberin (human pancreatic islet), N-acetyl-2-D-arginine-29-L-argininamide-30-de-L-glutamine-31-de-L-glutamine-32-deglycine-33-de-L-glutamic acid-34-de-L-serine-35-de-L-asparagine-36-de-L-glutamine-37-de-L-glutamic acid-38-de-L-arginine-39-deglycine-40-de-L-alanine-41-de-L-arginine-42-de-L-alanine-43-de-L-arginine-44-de-L-leucinamide-
SQL 29

SEQ 1 YRDAIFTNSY RKVLGQLSAR KLLQDIMSR
========== ========== =========
HITS AT: 1-29
NTE modified

type	------ location ------		description
terminal mod.	Tyr-1	-	N-acetyl
terminal mod.	Arg-29	-	C-terminal amide

FILE 'CAPLUS' ENTERED AT 15:05:21 ON 19 JUN 2002
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L3 65 SEA FILE=REGISTRY ABB=ON [YH][R'CIT']DA[IV].T[NQSTA'ABU''AIB'][R'HAR'K'ORN''CIT''NLE'YSA'AIB'][YF]R[K'ORN'][V'NLE'][L'NLE'][GA'ABU''NLE'Q][QR]L[S'NLE'][A'ABU']R[K'ORN'][LA'AIB']LQDI[ML'NLE''ABU'R][RSNDA'ABU'][R'HAR']/SQSP

L4 42 SEA FILE=CAPLUS ABB=ON L3

Registry File answer set crossed into CAPLUS to get citations

=> d ibib ab hitrn l4 1-42; fil hom

L4 ANSWER 1 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2002:52439 CAPLUS
DOCUMENT NUMBER: 136:210843
TITLE: Expression of a splice variant of the receptor for GHRH in 3T3 fibroblasts activates cell proliferation responses to GHRH analogs
AUTHOR(S): Kiaris, Hippokratis; Schally, Andrew V.; Busto, Rebeca; Halmos, Gabor; Artavanis-Tsakonas, Spyros; Varga, Jozsef L.
CORPORATE SOURCE: Harvard Medical School, Massachusetts General Hospital Cancer Center, Charlestown, MA, 02129, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2002), 99(1), 196-200
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The stimulatory effects of growth hormone-releasing hormone (GHRH) and the antiproliferative action of GHRH antagonists have been demonstrated in various cancers, but the receptors that mediate these responses are not clearly identified. Recently, we reported that human cancer cell lines express splice variants (SVs) of the receptors for GHRH. SV1 exhibits the greatest similarity to the pituitary GHRH receptor and is most likely to be functional. To ascertain whether SV1 mediates mitogenic effects on nonpituitary tissues, we expressed SV1 in 3T3 mouse fibroblasts and studied the properties of the transfected cells. Radioligand binding assays with 125I-labeled GHRH antagonist JV-1-42 detected high affinity (Kd = 0.58 nM) binding sites for GHRH with a maximal binding capacity (Bmax) of 103 fmol/mg of membrane protein in 3T3 cells transfected with pcDNA3-SV1, whereas the control cells transfected with the empty vector did not show any GHRH binding. Cell proliferation studies showed that cells expressing SV1 are much more sensitive to GHRH analogs than the pcDNA3 controls. Thus, the expression of SV1 augments the stimulatory responses to GHRH(1-29)NH2 or GHRH agonist JI-38 and inhibitory responses to GHRH antagonist JV-1-38 as compared with pcDNA3 controls. The stimulation of SV1-expressing cells by GHRH or JI-38 is followed by an increase in cAMP prodn., but no GH release occurs. Vasoactive intestinal peptide had no effect, and its antagonist JV-1-53 did not inhibit the proliferation of SV1-expressing cells stimulated by GHRH. Our results suggest that SV1 could mediate responses of nonpituitary cells and various tumors to GHRH and GHRH antagonists. The presence of SV1 in several human cancer cell lines provides a rationale for antitumor therapy based on the blockade of this receptor by specific GHRH antagonists.

IT **221377-58-8**, JV-1-42 - use Registry # to match citations to sequences
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(GHRH receptor splice variant expression in 3T3 fibroblasts activates cell proliferation responses to GHRH analogs)

REFERENCE COUNT: 33 THERE ARE 33 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:846672 CAPLUS
DOCUMENT NUMBER: 136:144824
TITLE: Inhibition of growth and metastases of MDA-MB-435 human estrogen-independent breast cancers by an antagonist of growth hormone-releasing hormone
AUTHOR(S): Chatzistamou, Ioulia; Schally, Andrew V.; Varga, Jozsef L.; Groot, Kate; Busto, Rebeca; Armatis, Patricia; Halmos, Gabor
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70112-1262, USA
SOURCE: Anti-Cancer Drugs (2001), 12(9), 761-768
CODEN: ANTDEV; ISSN: 0959-4973
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antagonists of growth hormone-releasing hormone (GH-RH) inhibit the growth of various cancers by mechanism(s) that include the suppression of the insulin-like growth factors (IGF)-I and/or -II. In this study, nude mice bearing orthotopic implants of MDA-MB-435 human estrogen-independent breast carcinoma received 39 days of therapy with GH-RH antagonist JV-1-36 (20 .mu.g/day). The treatment significantly inhibited tumor growth by 71.1% ($p<0.01$) and nullified the metastatic potential of MDA-MB-435 cells. Four of eight control mice (50%) developed metastases in the lymph nodes and one (12.5%) in the lung, but none of the animals receiving JV-1-36 showed metastatic spread. GH-RH antagonist JV-1-36 inhibited the growth of MDA-MB-435 cells in vitro, while IGF-I stimulated it. However, mRNA for IGF-I or -II was not detected in MDA-MB-435 cells, indicating that the suppression of autocrine IGFs may not be involved in the antiproliferative mechanism. Using ligand competition assays with 125I-labeled GH-RH antagonist JV-1-42, specific high-affinity binding sites for GH-RH were found on tumor membranes. Reverse transcription-polymerase chain reaction revealed the expression of mRNA for GH-RH receptor splice variant-1 in MDA-MB-435 tumors. Our results suggest that the antitumorigenic action of GH-RH antagonists on MDA-MB-435 breast cancer could be direct and mediated by tumoral GH-RH receptors.
IT **221377-79-3**, JV-1-36
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(inhibition of growth and metastases of MDA-MB-435 human estrogen-independent breast cancers by GHRH antagonist)
REFERENCE COUNT: 26 THERE ARE 26 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:723866 CAPLUS
DOCUMENT NUMBER: 136:877
TITLE: Antagonists of GHRH decrease production of GH and IGF-I in MXT mouse mammary cancers and inhibit tumor growth
AUTHOR(S): Szepeshazi, Karoly; Schally, Andrew V.; Armatis, Patricia; Groot, Kate; Hebert, Francine; Feil, Anita; Varga, Jozsef L.; Halmos, Gabor
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, 70112, USA
SOURCE: Endocrinology (2001), 142(10), 4371-4378
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

Searched by Barb O'Bryen, STIC 308-4291

AB The involvement of IGF-I in mammary carcinogenesis is well established, but the role of GH, as an autocrine growth factor for breast cancers is poorly understood. The goal of the authors' study was to investigate whether antagonists of GHRH can interfere with the effects of GH and IGF-I in MXT mouse mammary cancers. GHRH antagonists JV-1-36 and JV-1-38 inhibited growth of estrogen-independent MXT mouse mammary cancers in vivo, producing about 50% redn. in tumor vol. This growth inhibition was assocd. with a decrease in cell proliferation and an increase in apoptosis in MXT cancers. RIA and RT-PCR analyses showed that the concns. of GH and IGF-I and the levels of mRNA for GH and IGF-I in MXT tumors were reduced by the therapy with GHRH antagonists. The mRNA for GH receptors was also decreased. In vitro, the proliferation of MXT cancer cells was strongly stimulated by GH and less effectively by IGF-I, indicating that both GH and IGF-I may act as growth factors for this mammary carcinoma. GHRH antagonist JV-1-38 inhibited the autonomous growth of MXT cells and the proliferation induced by IGF-I or GH and diminished 3H-thymidine-incorporation stimulated by IGF-I and GH. These findings and a sustained increase in cyclin B2 concns. in the cells shown by immunoblotting indicate that JV-1-38 causes a block at the end of the G2 phase of cell cycle. The authors' results demonstrate that GHRH antagonists decrease the local prodn. of both GH and IGF-I in MXT mouse mammary cancers, the resulting growth inhibition being the consequence of reduced cell proliferation and increased apoptosis.

IT **221377-79-3**, JV-1-36
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(GHRH antagonists decrease prodn. of GH and IGF-I in MXT mouse mammary cancers and inhibit tumor growth)

REFERENCE COUNT: 50 THERE ARE 50 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 42 CAPLUS COPYRIGHT 2002 ACS

ACCESSION NUMBER: 2001:407258 CAPLUS
DOCUMENT NUMBER: 135:266764
TITLE: Antiproliferative actions of growth hormone-releasing hormone antagonists on MiaPaCa-2 human pancreatic cancer cells involve cAMP independent pathways
AUTHOR(S): Rekasi, Z.; Varga, J. L.; Schally, A. V.; Plonowski, A.; Halmos, G.; Csernus, B.; Armatis, P.; Groot, K.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70112, USA
SOURCE: Peptides (New York, NY, United States) (2001), 22(6), 879-886
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier Science Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB We evaluated the effects of GHRH antagonists on the proliferation of MiaPaCa-2 human pancreatic cancer cells and cAMP signaling in vitro. GHRH antagonists inhibited the proliferation of MiaPaCa-2 cells in vitro in a dose-dependent way and caused a significant elevation in cAMP prodn. In a superfusion system, short-term exposure of the cells to GHRH antagonists evoked an acute, dose-dependent release of cAMP into the medium. Native GHRH, which stimulates cAMP efflux from pituitary at nanomolar doses, did not influence cAMP release from cultured or superfused MiaPaCa-2 cells even at 10-30 .mu.M. VIP, PACAP, secretin and glucagon also did not influence cell proliferation or cAMP prodn. Adenylate cyclase activator forskolin (FSK) caused a greater cAMP response, but a smaller antiproliferative effect than GHRH antagonists. Combined treatment with FSK and GHRH antagonist JV-1-38 potentiated the cAMP-inducing effect of FSK, but did not produce a greater inhibition of cell proliferation than JV-1-38 alone. A selective accumulation of radiolabeled GHRH antagonist [125I]JV-1-42 in vivo in MiaPaCa-2 carcinoma xenografted into nude mice

was also obsd. In conclusion, second messengers other than cAMP participate in the signal transduction pathways of GHRH analogs mediated by tumoral GHRH receptors.

IT **221377-57-7**, MZ 6-55 **221377-79-3**, JV-1-36
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiproliferative actions of GHRH antagonists on MiaPaCa-2 human pancreatic cancer cells involve cAMP independent pathways)

IT **221377-58-8**, JV-1-42
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(antiproliferative actions of GHRH antagonists on MiaPaCa-2 human pancreatic cancer cells involve cAMP independent pathways)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 5 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2001:367559 CAPLUS
DOCUMENT NUMBER: 135:102703
TITLE: Antagonists of growth hormone-releasing hormone and somatostatin analog RC-160 inhibit the growth of the OV-1063 human epithelial ovarian cancer cell line xenografted into nude mice
AUTHOR(S): Chatzistamou, Ioulia; Schally, Andrew V.; Varga, Jozsef L.; Groot, Kate; Armatis, Patricia; Busto, Rebeca; Halmos, Gabor
CORPORATE SOURCE: Endocrine, Polypeptide, Veterans Affairs Medical Center, Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70112, USA
SOURCE: Journal of Clinical Endocrinology and Metabolism (2001), 86(5), 2144-2152
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effects of antagonists of GHRH and the somatostatin analog RC-160 on the growth of OV-1063 human epithelial ovarian cancer cells xenografted into nude mice were investigated. Treatment with 20 .mu.g/day of the GHRH antagonist JV-1-36 or MZ-5-156 and 60 .mu.g/day of the somatostatin analog RC-160 for 25 days decreased tumor vol. by 70.9% ($P < 0.01$), 58.3% ($P < 0.05$), and 60.6% ($P < 0.01$), resp., vs. the control value. The levels of GH in serum were decreased in all of the treated groups, but only RC-160 significantly reduced serum insulin-like growth factor I (IGF-I). The levels of mRNA for IGF-I and -II and for their receptors in OV-1063 tumors were investigated by multiplex RT-PCR. No expression of mRNA for IGF-I was detected, but treatment with JV-1-136 caused a 51.8% decrease ($P < 0.05$) in the level of mRNA for IGF-II in tumors. Exposure of OV-1063 cells cultured in vitro to GHRH, IGF-I, or IGF-II significantly ($P < 0.05$) stimulated cell growth, but 10-5 M JV-1-36 nearly completely inhibited ($P < 0.001$) OV-1063 cell proliferation. OV-1063 tumors expressed mRNA for GHRH receptors and showed the presence of binding sites for GHRH. Our results indicate that antagonistic analogs of GHRH and the somatostatin analog RC-160 inhibit the growth of epithelial ovarian cancers. The effects of RC-160 seem to be exerted more on the pituitary GH-hepatic IGF-I axis, whereas GHRH antagonists appear to reduce IGF-II prodn. and interfere with the autocrine regulatory pathway. The antitumorigenic action of GHRH antagonists appears to be mediated by GHRH receptors found in OV-1063 tumors.

IT **221377-79-3**, JV-1-36
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists of growth hormone-releasing hormone and somatostatin analog RC-160 inhibit the growth of OV-1063 human epithelial ovarian

cancer cell line xenografted into nude mice)
REFERENCE COUNT: 49 THERE ARE 49 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:829867 CAPLUS
DOCUMENT NUMBER: 134:216921
TITLE: Suppression of tumor growth by growth hormone-releasing hormone antagonist JV-1-36 does not involve the inhibition of autocrine production of insulin-like growth factor II in H-69 small cell lung carcinoma
AUTHOR(S): Kiaris, H.; Schally, A. V.; Varga, J. L.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, New Orleans, LA, 70112-1262, USA
SOURCE: Cancer Letters (Shannon, Ireland) (2000), 161(2), 149-155
CODEN: CALEDQ; ISSN: 0304-3835
PUBLISHER: Elsevier Science Ireland Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Although a high antitumor activity of growth hormone releasing hormone (GHRH) antagonists has been demonstrated in various tumors, the mechanism of action of these peptide analogs remains poorly understood. An assocn. has been obsd. between the antitumor effects of GHRH antagonists and the inhibition of insulin-like growth factors (IGFs), but it is not clear whether the suppression of IGFs is obligatory for the action of GHRH antagonists. In the present study we investigated various components of the IGF system in H-69 small cell lung carcinoma (SCLC) xenografted into nude mice and treated with GHRH antagonist JV-1-36. After 31 days of treatment with JV-1-36, tumor wt. was inhibited by about 70% as compared with the controls. Reverse transcription-polymerase chain reaction (RT-PCR) anal. indicated that H-69 tumors express mRNAs for IGF-II and IGF-receptors- (IGFR-) I and II, but not for IGF-I. The levels of mRNA for IGF-II and IGFR-I and -II were not affected by the treatment with JV-1-36. Exposure to antibody IRa, which blocks the binding of IGF-I and -II to IGFR-I, inhibited the proliferation of H-69 cells in vitro, indicating that IGF-II present in the tumors might stimulate the proliferation of H-69 SCLC in an autocrine manner. Collectively our results suggest that inhibition of tumor growth by GHRH antagonists is not assocd. with the suppression of the autocrine stimulation by IGF-II in H-69 SCLC.
IT **221377-79-3**, JV-1-36
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(mechanism of tumor growth suppression by growth hormone-releasing hormone antagonist JV-1-36)
REFERENCE COUNT: 24 THERE ARE 24 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:824291 CAPLUS
DOCUMENT NUMBER: 134:21425
TITLE: Protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components
INVENTOR(S): Bridon, Dominique P.; Ezrin, Alan M.; Milner, Peter G.; Holmes, Darren L.; Thibaudeau, Karen
PATENT ASSIGNEE(S): Conjuchem, Inc., Can.
SOURCE: PCT Int. Appl., 733 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 3
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000069900	A2	20001123	WO 2000-US13576	20000517
WO 2000069900	A3	20010215		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2000070665	A2	20001123	WO 2000-IB763	20000517
WO 2000070665	A3	20010419		
W: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1105409	A2	20010613	EP 2000-936023	20000517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
EP 1171582	A2	20020116	EP 2000-929748	20000517
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				

PRIORITY APPLN. INFO.:			
US 1999-134406P	P	19990517	
US 1999-153406P	P	19990910	
US 1999-159783P	P	19991015	
WO 2000-IB763	W	20000517	
WO 2000-US13576	W	20000517	

AB A method for protecting a peptide from peptidase activity in vivo, the peptide being composed of between 2 and 50 amino acids and having a C-terminus and an N-terminus and a C-terminus amino acid and an N-terminus amino acid is described. In the first step of the method, the peptide is modified by attaching a reactive group to the C-terminus amino acid, to the N-terminus amino acid, or to an amino acid located between the N-terminus and the C-terminus, such that the modified peptide is capable of forming a covalent bond in vivo with a reactive functionality on a blood component. The solid phase peptide synthesis of a no. of derivs. with 3-maleimidopropionic acid (3-MPA) is described. In the next step, a covalent bond is formed between the reactive group and a reactive functionality on a blood component to form a peptide-blood component conjugate, thereby protecting said peptide from peptidase activity. The final step of the method involves the analyzing of the stability of the peptide-blood component conjugate to assess the protection of the peptide from peptidase activity. Thus, the percentage of a K5 kringle peptide (Pro-Arg-Lys-Leu-Tyr-Asp-Lys-NH2) conjugated to human serum albumin via MPA remained relatively const. through a 24-h plasma assay in contrast to unmodified K5 which decreased to 9% of the original amt. of K5 in only 4 h in plasma.

IT **309244-12-0**
RL: PRP (Properties)
(unclaimed sequence; protection of endogenous therapeutic peptides from peptidase activity through conjugation to blood components)

L4 ANSWER 8 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:664852 CAPLUS
DOCUMENT NUMBER: 133:348337
TITLE: Human renal cell carcinoma expresses distinct binding sites for growth hormone-releasing hormone
AUTHOR(S): Halmos, Gabor; Schally, Andrew V.; Varga, Jozsef L.; Plonowski, Artur; Rekasi, Zoltan; Czompoly, Tamas
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA, 70112-2699, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(19), 10555-10560
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Antagonists of growth hormone-releasing hormone (GHRH) inhibit the proliferation of various human cancers in vitro and in vivo by mechanisms that include apparent direct effects through specific binding sites expressed on tumors and that differ from pituitary human GHRH (hGHRH) receptors. In this study, GHRH antagonist JV-1-38 (20 .mu.g/day per animal s.c.) inhibited the growth of orthotopic CAKI-1 human renal cell carcinoma (RCC) by 83% and inhibited the development of metastases to lung and lymph nodes. Using ligand competition assays with 125I-labeled GHRH antagonist JV-1-42, the authors demonstrated the presence of specific high-affinity (Kd = 0.25 nM) binding sites for GHRH with a maximal binding capacity (Bmax) of 70.2 fmol/mg of membrane protein in CAKI-1 tumors. These receptors bind GHRH antagonists preferentially and display a lower affinity for hGHRH. The binding of 125I-JV-1-42 is not inhibited by vasoactive intestinal peptide (VIP)-related peptides sharing structural homol. with hGHRH. The receptors for GHRH antagonists on CAKI-1 tumors are distinct from binding sites detected with 125I-VIP (Kd = 0.89 nM; Bmax = 183.5 fmol/mg of protein) and also have different characteristics from GHRH receptors on rat pituitary as documented by the insignificant binding of [His1,125I-Tyr10,Nle27]hGHRH(1-32)NH2. Reverse transcription-PCR revealed the expression of splice variants of hGHRH receptor in CAKI-1 RCC. Biodistribution studies demonstrate an in vivo uptake of 125I-JV-1-42 by the RCC tumor tissue. The presence of specific receptor proteins that bind GHRH antagonists in CAKI-1 RCC supports the view that distinct binding sites that mediate the inhibitory effect of GHRH antagonists are present on various human cancers.

IT **221377-58-8**, JV 1-42 **221377-79-3**, JV 1-36
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(human renal cell carcinoma expresses distinct binding sites for growth hormone-releasing hormone and antagonists distinct from growth hormone-releasing hormone receptor)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:545266 CAPLUS
DOCUMENT NUMBER: 134:240
TITLE: Antagonists of growth hormone-releasing hormone inhibit the growth of U-87MG human glioblastoma in nude mice
AUTHOR(S): Kiaris, Hippokratis; Schally, Andrew V.; Varga, Jozsef L.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center and Section of Experimental Medicine, Department of Medicine, Tulane University

Searched by Barb O'Bryen, STIC 308-4291

School of Medicine, New Orleans, LA, USA
SOURCE: Neoplasia (New York) (2000), 2(3), 242-250
CODEN: NEOPFL; ISSN: 1522-8002
PUBLISHER: Nature America Inc.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antagonists of growth hormone-releasing hormone(GH-RH)inhibit the growth of various cancers by mechanisms that involve the suppression of the insulin-like growth factor (IGF)-I and/or IGF-II. In view of the importance of the IGF system in glioma tumorigenesis, the effects of GH-RH antagonists MZ-5-156 and JV-1-36 were investigated in nude mice bearing s.c. and ortho-topic xenografts of U-87MG human glioblastomas. After 4 wk of therapy with MZ-5-156 or JV-1-36 at the dose of 20 .mu.g/day per animal, the final vol. of s.c. U-87MG tumors was significantly ($P < .01$) decreased by 84% and 76%, resp., as compared with controls. Treatment with GH-RH antagonists also reduced tumor wt. and the levels of mRNA for IGF receptor type I (IGFR-I). A redn. in the mRNA levels for IGF-II was found in tumors of mice treated with MZ-5-156. Treatment with MZ-5-156 or JV-1-36 also extended the survival of nude mice implanted ortho-topically with U-87MG glioblastomas by 81% ($P < .005$) and 18%, resp., as compared with the controls. Exposure in vitro to GH-RH antagonists MZ-5-156 or JV-1-36 at 1 .mu.M concn. for 24 h decreased the tumorigenicity of U-87MG cells in nude mice by 10% to 30% and extended the latency period for the development of s.c. palpable tumors by 31% to 56%, as compared with the controls. Exposure of U-87MG cells to GH-RH antagonists in vitro also resulted in a time-dependent increase in the mRNA levels of IGFR-II or a decrease in the mRNA levels of IGFR-I. MRNA for GH-RH was detected in U-87MG cells and xenografts implying that GH-RH may play a role in the pathogenesis of this tumor. Our results suggest that GH-RH antagonists MZ-5-156 and JV-1-36 inhibit the growth of U-87MG human glioblastoma by mechanisms that involve the suppression of IGF system. Antagonistic analogs of GH-RH merit further development for the treatment of malignant glioblastoma.
IT **221377-79-3**, JV 1-36
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(antagonists of GHRH inhibit growth of human glioblastoma in nude mice)
REFERENCE COUNT: 31 THERE ARE 31 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 10 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:521514 CAPLUS
DOCUMENT NUMBER: 133:217935
TITLE: Antagonists of growth hormone-releasing hormone and vasoactive intestinal peptide inhibit tumor proliferation by different mechanisms: evidence from in vitro studies on human prostatic and pancreatic cancers
AUTHOR(S): Rekasi, Zoltan; Varga, Jozsef L.; Schally, Andrew V.; Halmos, Gabor; Armatis, Patricia; Groot, Kate; Czompoly, Tamas
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, and Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70112, USA
SOURCE: Endocrinology (2000), 141(6), 2120-2128
CODEN: ENDOAO; ISSN: 0013-7227
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antagonists of GH-releasing hormone (GHRH) and vasoactive intestinal peptide (VIP) inhibit the proliferation of various tumors in vitro and in vivo, but a comparison of their antitumor effects and mechanisms of action has not been reported to date. The authors recently synthesized and

characterized a series of analogs, some of which are primarily GHRH antagonists (JV-1-36, JV-1-38, and JV-1-42), whereas others are more selective for VIP receptors (VPAC-R; JV-1-50, JV-1-51, JV-1-52, and JV-1-53). LNCaP human prostatic cancer cells express VPAC-R, with predominant subtype 1 detd. by RT-PCR. The authors' studies show that GHRH antagonists significantly inhibit the proliferation of both VPAC-R pos. LNCaP cells ($P < 0.001$) and VPAC-R neg. MiaPaCa-2 human pancreatic cancer cells cultured in vitro ($P < 0.05$ to $P < 0.001$). Growth inhibition of LNCaP cells is accompanied by a proportional redn. in prostate-specific antigen (PSA) secretion ($P < 0.001$). In a superfusion system, the inhibitory activities of the analogs on the rate of VIP and GHRH-induced PSA secretion correlate well with their VPAC-R binding affinities to LNCaP cell membranes. Antagonists more selective for VPAC-R display a stronger inhibition of inducible PSA release than GHRH antagonists, but have smaller effects or no effects on proliferation and PSA secretion in culture. Collectively, the authors' findings demonstrate that the antiproliferative activity of the analogs on cancer cells is not correlated to their VPAC-R antagonistic potencies. Because GHRH antagonists inhibit the proliferation of LNCaP cells more powerfully than VPAC-R antagonists and also suppress the growth of VPAC-R-neg. MiaPaCa-2 cells, it can be concluded that their antiproliferative effect is exerted through a mechanism independent of VPAC-R.

IT **221377-58-8 221377-59-9 221377-79-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(GH-RH antagonists inhibit tumor proliferation more powerfully than VIP receptor antagonists suggesting VIP receptor independent mechanism in human prostatic and pancreatic cancer cell lines)

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 11 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:430815 CAPLUS
DOCUMENT NUMBER: 133:290719
TITLE: Antagonists of growth hormone-releasing hormone arrest the growth of MDA-MB-468 estrogen-independent human breast cancers in nude mice
AUTHOR(S): Kahan, Zsuzsanna; Varga, Jozsef L.; Schally, Andrew V.; Rekasi, Zoltan; Armatis, Patricia; Chatzistamou, Ioulia; Czompoly, Tamas; Halmos, Gabor
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, USA
SOURCE: Breast Cancer Research and Treatment (2000), 60(1), 71-79
CODEN: BCTRD6; ISSN: 0167-6806
PUBLISHER: Kluwer Academic Publishers
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Since antagonists of growth hormone-releasing hormone (GH-RH) inhibit proliferation of various tumors, in this study we investigated the effects of GH-RH antagonists MZ-5-156 or JV-1-36 on growth of estrogen-independent MDA-MB-468 human breast cancers xenografted into nude mice. Both GH-RH antagonists administered at a dose of 20 .mu.g/day induced regression of some and growth arrest of other tumors, while control tumors continued to grow. After 5 wk of therapy with MZ-5-156 or JV-1-36, final vol. and wt. of MDA-MB-468 tumors were significantly decreased (all p values < 0.001) and serum IGF-I levels as well as tumor IGF-I mRNA expression were reduced as compared with controls. High affinity binding sites for IGF-I were detected by the ligand binding method. Gene expression of human IGF-I receptors, as measured by the RT-PCR, was not significantly different in control and treated MDA-MB-468 tumors. In cell culture, IGF-I did not stimulate, GH-RH slightly stimulated, while MZ-5-156 and JV-1-36 inhibited

proliferation of MDA-MB-468 cells known to possess defective insulin and IGF-I receptor signaling. The expression of mRNA for human GH-RH was found in five of 8 tumors treated with GH-RH antagonists, and in one of the five control tumors. These results suggest that GH-RH antagonists inhibit MDA-MB-468 breast cancers possibly through mechanisms involving interference with locally produced GH-RH.

IT **221377-79-3**, JV 1-36
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(221377793; GH-RH antagonists inhibition of estrogen-independent human breast cancer)

REFERENCE COUNT: 40 THERE ARE 40 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 12 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:384335 CAPLUS
DOCUMENT NUMBER: 133:130085
TITLE: Antagonists of growth hormone-releasing hormone (GH-RH) inhibit IGF-II production and growth of HT-29 human colon cancers
AUTHOR(S): Szepeshazi, K.; Schally, A. V.; Groot, K.; Armatis, P.; Halmos, G.; Hebert, F.; Szende, B.; Varga, J. L.; Zarandi, M.
CORPORATE SOURCE: Veterans Affairs Medical Center, Endocrine, Polypeptide and Cancer Institute, New Orleans, LA, 70112-1262, USA
SOURCE: British Journal of Cancer (2000), 82(10), 1724-1731
CODEN: BJCAAI; ISSN: 0007-0920
PUBLISHER: Harcourt Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Insulin-like growth factors (IGFs) I and II are implicated in progression of various tumors including colorectal carcinomas. To interfere with the prodn. of IGFs, the authors treated male nude mice bearing xenografts of HT-29 human colon cancer with various potent growth hormone-releasing hormone (GH-RH) antagonists. Twice daily injections of antagonist MZ-4-71, 10 .mu.g i.p. or 5 .mu.g s.c. resulted in a significant 43-45% inhibition of tumor growth. Longer acting GH-RH antagonists, MZ-5-156 and JV-1-36 given once daily at doses of 20 .mu.g s.c. produced a 43-58% decrease in vol. and wt. of cancers. Histol. analyses of HT-29 cancers demonstrated that both a decreased cell proliferation and an increased apoptosis contributed to tumor inhibition. GH-RH antagonists did not change serum IGF-I or IGF-II levels, but significantly decreased IGF-II concn. and reduced mRNA expression for IGF-II in tumors. In vitro studies showed that HT-29 cells produced and secreted IGF-II into the medium, and addn. of MZ-5-156 dose-dependently decreased IGF-II prodn. by about 40% as well as proliferation of HT-29 cells. The authors' studies demonstrate that GH-RH antagonists inhibit growth of HT-29 human colon cancers in vivo and in vitro. The effect of GH-RH antagonists may be mediated through a reduced prodn. and secretion of IGF-II by cancer cells.

IT **190791-06-1 286850-19-9**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists of growth hormone-releasing hormone inhibit IGF-II prodn. and growth of HT-29 human colon cancers)

REFERENCE COUNT: 44 THERE ARE 44 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 13 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:284018 CAPLUS
DOCUMENT NUMBER: 132:303894

TITLE: Antagonistic analogs of GH-RH inhibiting IGF-I and -II
INVENTOR(S): Schally, Andrew V.; Varga, Jozsef; Zarandi, Marta
PATENT ASSIGNEE(S): The Administrators of the Tulane Educational Fund, USA
SOURCE: U.S., 17 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6057422	A	20000502	US 1998-199381	19981125
WO 2000031136	A1	20000602	WO 1999-US27822	19991123
W: AU, BG, BR, BY, CA, CN, CZ, EE, GE, HR, HU, ID, IL, IN, IS, JP, KG, KR, KZ, LT, LV, MK, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TR, UA, UZ, YU, ZA, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
BR 9915512	A	20010807	BR 1999-15512	19991123
EP 1133522	A1	20010919	EP 1999-963962	19991123
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
NO 2001002489	A	20010704	NO 2001-2489	20010521

PRIORITY APPLN. INFO.: US 1998-199381 A 19981125
WO 1999-US27822 W 19991123
OTHER SOURCE(S): MARPAT 132:303894

AB There is provided a novel series of synthetic analogs of hGH-RH(1-29) NH2. These analogs inhibit the activity of endogenous hGH-RH, and therefore prevent the release of growth hormone. The stronger inhibitory potencies of the new analogs, as compared to previously described ones, results from replacement of various amino acids. The GH-RH antagonists are effective in treating cancer, for example human cancers of the breast, lung, colon, brain, pancreas, and prostate where the receptors for IGF-I or IGF-II are present.

IT **221377-28-2P 221377-49-7P 221377-52-2P**
221377-57-7P 221377-58-8P 221377-59-9P
221377-60-2P 221377-76-0P 221377-77-1P
221377-78-2P 221377-79-3P 221377-80-6P
265307-63-9P 265307-91-3P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of antagonistic analogs of GH-RH inhibiting IGF-I and -II for use in treating cancer)

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 14 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 2000:99362 CAPLUS
DOCUMENT NUMBER: 132:217257
TITLE: Antagonistic actions of analogs related to growth hormone-releasing hormone (GHRH) on receptors for GHRH and vasoactive intestinal peptide on rat pituitary and pineal cells in vitro
AUTHOR(S): Rekasi, Zoltan; Varga, Jozsef L.; Schally, Andrew V.; Halmos, Gabor; Groot, Kate; Czompoly, Tamas
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, and Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70112, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (2000), 97(3), 1218-1223

Searched by Barb O'Bryen, STIC 308-4291

CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Peptide analogs of growth hormone-releasing hormone (GHRH) can potentially interact with vasoactive intestinal peptide (VIP) receptors (VPAC1-R and VPAC2-R) because of the structural similarities of these two hormones and their receptors. The authors synthesized four new analogs related to GHRH (JV-1-50, JV-1-51, JV-1-52, and JV-1-53) with decreased GHRH antagonistic activity and increased VIP antagonistic potency. To characterize various peptide analogs for their antagonistic activity on receptors for GHRH and VIP, the authors developed assay systems based on superfusion of rat pituitary and pineal cells. Receptor-binding affinities of peptides to the membranes of these cells were also evaluated by radioligand competition assays. Previously reported GHRH antagonists JV-1-36, JV-1-38, and JV-1-42 proved to be selective for GHRH receptors, because they did not influence VIP-stimulated VPAC2 receptor-dependent prolactin release from pituitary cells or VPAC1 receptor-dependent cAMP efflux from pinealocytes but strongly inhibited GHRH-stimulated growth hormone (GH) release. Analogs JV-1-50, JV-1-51, and JV-1-52 showed various degrees of VPAC1-R and VPAC2 antagonistic potency, although also preserving a substantial GHRH antagonistic effect. Analog JV-1-53 proved to be a highly potent VPAC1 and VPAC2 receptor antagonist, devoid of inhibitory effects on GHRH-evoked GH release. The antagonistic activity of these peptide analogs on processes mediated by receptors for GHRH and VIP was consistent with the binding affinity. The analogs with antagonistic effects on different types of receptors expressed on tumor cells could be utilized for the development of new approaches to treatment of various human cancers.
IT **221377-58-8 221377-59-9 221377-79-3**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); THU (Therapeutic use); BIOL (Biological study); PROC (Process); USES (Uses)
(antagonistic actions of GHRH analogs on receptors for GHRH and VIP in rat pituitary and pineal cells in vitro)
REFERENCE COUNT: 37 THERE ARE 37 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 15 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1999:63483 CAPLUS
DOCUMENT NUMBER: 130:247129
TITLE: Synthesis and biological evaluation of antagonists of growth hormone-releasing hormone with high and protracted in vivo activities; (inhibitors of GH release/structure-activity relationships/cancer therapy)
AUTHOR(S): Varga, Jozsef L.; Schally, Andrew V.; Csernus, Valer J.; Zarandi, Marta; Halmos, Gabor; Groot, Kate; Rekasi, Zoltan
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70112, USA
SOURCE: Proceedings of the National Academy of Sciences of the United States of America (1999), 96(2), 692-697
CODEN: PNASA6; ISSN: 0027-8424
PUBLISHER: National Academy of Sciences
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Some antagonists of human growth hormone-releasing hormone (hGH-RH) synthesized previously were shown to inhibit in vivo proliferation of various human cancers in nude mice. However, the activity of these analogs requires an increase to assure clin. efficacy. In an attempt to

prep. hGH-RH antagonists with a high and protracted activity, we synthesized and biol. tested 22 antagonistic analogs of hGH-RH(1-29)NH2. The ability of the antagonists to inhibit hGH-RH-induced GH release was evaluated in vitro in a superfused rat pituitary system, as well as in vivo after i.v. injection into rats. The binding affinity of the peptides to GH-RH receptors also was detd. All antagonistic analogs had the common core sequence [PhAc-Tyr1,D-Arg2, Phe(4-Cl)6 (para-chlorophenylalanine), Abu15 (.alpha.-aminobutyric acid),Nle27]hGH-RH(1-29)NH2 and contained Arg, D-Arg, homoarginine (Har), norleucine (Nle), and other substitutions. The following analogs were detd. to have a high and/or protracted antagonistic activity: [PhAc-Tyr1,D-Arg2,Phe(4-Cl)6,Arg9,Abu15,Nle27,D-Arg29]hGH-RH(1-29)NH2 (JV-1-10), [PhAc-Tyr1,D-Arg2,Phe(4-Cl)6,Abu15,Nle27, D-Arg28,Har29]hGH-RH(1-29)NH2 (MZ-6-55), [PhAc-Tyr1,D-Arg2,Phe(4-Cl)6,Arg9,Abu15,Nle27,D-Arg28,Har29]hGH-RH(1-29)NH2 (JV-1-36), and [PhAc-Tyr1,D-Arg2,Phe(4-Cl)6,Har9,Tyr(Me)10,Abu15,Nle27,D-Arg28,Har29]hGH-RH(1-29)NH2 (JV-1-38). Among the peptides tested, analog JV-1-36 showed the highest GH-RH antagonistic activity in vitro and also induced a strong and prolonged inhibition of GH release in vivo for at least 30 min. The antagonist JV-1-38 was slightly less potent than JV-1-36 both in vitro and in vivo but proved to be very long-acting in vivo, suppressing the GH-RH-induced GH release even after 60 min. High and protracted in vivo activities of these antagonists indicate an improvement over earlier GH-RH analogs. Some of these hGH-RH antagonists could find clin. applications in the treatment of cancers dependent on insulin-like growth factors I and II.

IT **221377-16-8P 221377-28-2P 221377-30-6P**
221377-46-4P 221377-49-7P 221377-52-2P
221377-57-7P 221377-58-8P 221377-59-9P
221377-60-2P 221377-76-0P 221377-77-1P
221377-78-2P 221377-79-3P 221377-80-6P
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); PRP (Properties); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(synthesis and biol. evaluation of antagonists of growth hormone-releasing hormone with high and protracted in vivo activities)

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 16 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:597995 CAPLUS
DOCUMENT NUMBER: 130:25311
TITLE: Synthesis and in vitro biological activities of new potent GH-RH antagonists with citrulline substitutions
AUTHOR(S): Zarandi, Marta; Kovacs, Magdolna; Horvath, Judit E.; Halmos, Gabor; Groot, Kate; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Tulane University, New Orleans, LA, 70146, USA
SOURCE: Peptides 1996, Proceedings of the European Peptide Symposium, 24th, Edinburgh, Sept. 8-13, 1996 (1998), Meeting Date 1996, 933-934. Editor(s): Ramage, Robert; Epton, Roger. Mayflower Scientific: Kingswinford, UK.
CODEN: 66RCA5
DOCUMENT TYPE: Conference
LANGUAGE: English

AB A symposium report on the prepn. and gonadotropin hormone antagonistic activity of citrulline-contg. analogs.

IT **216368-91-1P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activities of new potent GH-RH antagonists with

citrulline substitutions)
REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 17 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1998:93875 CAPLUS
DOCUMENT NUMBER: 128:239546
TITLE: New analogs of human growth hormone-releasing hormone (1-29) with high and prolonged antagonistic activity
AUTHOR(S): Toth, Katalin; Kovacs, Magdolna; Zarandi, Marta; Halmos, Gabor; Groot, Kate; Nagy, Attila; Kele, Zoltan; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Affairs Medical Center, Tulane University School of Medicine, New Orleans, LA, USA
SOURCE: Journal of Peptide Research (1998), 51(2), 134-141
CODEN: JPERFA; ISSN: 1397-002X
PUBLISHER: Munksgaard International Publishers Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Based on the authors' previous results, in conjunction with various structural considerations, 19 new analogs of the GHRH antagonist [PhAc-Tyr1,D-Arg2,Phe(pCl)6,Abu15,Nle27,Agm29]hGHRH(1-29) (MZ-5-156) were synthesized by the solid-phase method. These compds. were designed to develop further analogs of this class with increased receptor-binding affinity. All analogs had Abu15 and Nle27 modifications and were acylated with phenylacetic acid at the N-terminus. Most of the analogs had D-Arg2 and Phe(pCl)6 substituents and Agm29 or Arg29-NH2 at the C-terminus. Addnl. single substitutions consisted of the incorporation of D- or L-Tic1, D-Tic2, Tic6 or Phe(pNO2)6 and Arg29-NH2. The Arg29-NH2 analog of MZ-5-156 (KT-48) was further modified by single substitutions using Pal1; D-Tpi2; D- or L-Phe4; Phe(pX)6 X = F, Cl, I; Tyr7; Aib8; Tyr(Me)10 or Phe(pCl)10. Four peptides had multiple substitutions. All the analogs were evaluated for their ability to inhibit GH release induced by hGHRH(1-29)NH2 in vitro and some were also tested in vivo. Peptides [PhAc-Tyr1,D-Arg2,Phe(pI)6,Abu15,Nle27]hGHRH(1-29)NH2 (KT-30), [PhAc-Tyr1,D-Arg2,Phe(pCl)6,Aib8,Abu15,Nle27]hGHRH(1-29)NH2 (KT-50) and [PhAc-Tyr1,D-Arg2,Phe(pCl)6,Tyr(Me)10,Abu15,Nle27]hGHRH(1-29)NH2 (KT-40) with Phe(pI)6, Aib8 or Tyr(Me)10 modifications, resp., showed high and prolonged inhibitory effect in superfused rat pituitary system. Analog KT-50 also exhibited a strong and long-term inhibitory activity in vivo in rats. Most of the new analogs showed high binding affinities to rat pituitary GHRH receptors.
IT **204767-60-2 204767-61-3 204866-79-5 204866-80-8 204866-81-9 204866-82-0 204866-83-1 204866-84-2**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(new analogs of human growth hormone-releasing hormone (1-29) with high and prolonged antagonistic activity)

L4 ANSWER 18 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:746077 CAPLUS
DOCUMENT NUMBER: 127:359122
TITLE: Preparation of hGH-RH(1-29)NH2 analogs having antagonistic activity
INVENTOR(S): Schally, Andrew V.; Zarandi, Marta; Toth, Katalin
PATENT ASSIGNEE(S): Administrators of the Tulane Educational Fund, USA; Schally, Andrew V.; Zarandi, Marta; Toth, Katalin
SOURCE: PCT Int. Appl., 52 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent

LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9742223	A1	19971113	WO 1997-US7452	19970502
W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5942489	A	19990824	US 1996-642472	19960503
ZA 9703793	A	19971119	ZA 1997-3793	19970502
AU 9731172	A1	19971126	AU 1997-31172	19970502
EP 914340	A1	19990512	EP 1997-926399	19970502
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
JP 2001501585	T2	20010206	JP 1997-540054	19970502

PRIORITY APPLN. INFO.: US 1996-642472 A 19960503
WO 1997-US7452 W 19970502

OTHER SOURCE(S): MARPAT 127:359122

AB Title peptides X-R1-R2-R3-R4-R5-R6-Thr-R8-R9-R10-R11-R12 -Val-Leu-R15-Gln-Leu-Ser-R19-R20-R21-Leu-Leu-Gln-Asp-Ile-R27-R28-R29 [X = H, Ac, anthraquinone-2-carbonyl (Aqc), iodoacetyl (IAc), bromopropionyl (BrProp), OHC, isobutyryl (Ibu), 1- or 2-naphthylacetyl (Nac), 1- or 2-naphthoyl (Npt), 1- or 2-naphthylpropionyl (Npr), phenylacetyl (PhAc), 3-phenylpropionyl (Fpr), other arom. or nonpolar acyl group; R1 = Tyr, His, Phe(Y); Y = H, F, Cl, Br, NO2, NH2, Me, OMe; R2 = D-Arg, D-Cit, D-Har, D-Lys, D-Tic, D-Orn, R3 = Asp, D-Asp, Ala, D-Ala, Gly; R4 = Ala, Abu, Gly; R5 = Ile, Ala, Gly, R6 = Phe, Tic, Ala, Pro, Tpi, Nal, Phe(Y); R8 = Asn, Gln, Ser, Thr, Val, Leu, Ile, Ala, D-Ala, D-Asn, D-Gln, D-Thr, D-Leu, Abu, D-Abu, Nle, Aib; R9 = Ser; R10 = Tyr or Phe(Y); R11 = Arg, D-Arg, Cit, R12 = Lys, D-Lys, Cit, D-Cit, Orn, D-Orn, Nle, Ala; R15 = Gly, Ala, Abu, Gln; R19 = Ala, Abu; R20 = Arg, D-Arg, Cit; R21 = Lys, D-Lys, Orn, Cit; R27 = Met, Nle, Abu; R28 = Ser, Asn, Asp, Ala, Abu; R29 = Agm, Arg-NH2, Arg-OH, Cit-NH2, Cit-OH, Har-NH2, Har-OH; Abu = 2-aminobutanoyl; Agm = agmatine, Cit = citrulline; Har = homoarginine, Nal = 2-naphthylalanine, Tic = 1,2,3,4-tetrahydroisoquinoline-2-carbonyl, Tpi = 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-3-carbonyl], and pharmaceutically acceptable salts thereof, are prepd. and claimed as growth hormone release inhibitors and antitumor agents. Also claimed are cyclic peptides X-A1-B2-A3-R4-R5-R6-Thr-A8-Ser-R10-R11-B12-Val-Leu-R15-A16-A17-Ser-R19-B20-B21-Leu-Leu-Gln-A25-Ile-R27-R28-B29 [X, R4, R5, R10, R15, R27, R28, = as above; A = Glu, D-Glu, Gln, Asp, D-Asp, Asn, Abu, Leu, Tyr, His, Phe(Y); Y = H, F, Cl, Br, NO2, NH2, Me, OMe, Ser, Thr, Val, Ile, Ala, D-Ala, D-Asn, D-Gln, D-Thr, D-Leu, Abu, D-Abu, Nle, Aib; B = Lys, D-Lys, Arg, D-Arg, Orn, D-Orn, Agm; R6 = Phe, Tic, Tpi, Nal, Phe(Y); Y = H, F, Cl, Br, NO2, NH2, Me, OMe], and pharmaceutically acceptable salts thereof, wherein a lactam bridge is formed between any pairs of positions 1,2; 2,3; 8,12; 16,20; 17-21, 21,25; 25,29; or both 8,12 and 21,25. Thus, peptide PhAc-Tyr-D-Arg-Asp-Ala-Ile-Phe(pCl)-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-Ser-Agm (I) was prepd. by std. solid-phase methods on an aminomethyl resin using tert-butoxycarbonyl (Boc) N.alpha.-protection. I antagonized hGH-RH with Ki = 0.0159 nM in an in vitro test, and in an antitumor test, treatment of 10 .mu.g I per day resulted in significant inhibition of growth of SW-1990 tumors in nude mice.

IT **190783-58-5P 190783-59-6P 190791-06-1P 190791-08-3P 190975-94-1P 198404-60-3P**

RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of human growth hormone releasing factor analogs having antagonistic activity)

L4 ANSWER 19 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:294814 CAPLUS
DOCUMENT NUMBER: 127:29205
TITLE: Inhibition of GH release in rats by new potent antagonists of growth hormone-releasing hormone (GH-RH)
AUTHOR(S): Kovacs, Magdolna; Schally, Andrew V.; Zarandi, Marta; Groot, Kate
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute, Veterans Administration Medical Center and Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70146, USA
SOURCE: Peptides (Tarrytown, New York) (1997), 18(3), 431-438
CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Biol. activity of a new series of potent GH-RH antagonists contg. formyl or phenylacetyl group at the N-terminus of the sequence [D-Arg2,Phe(4-Cl)6,Nle27]hGH-RH(1-29)NH2, as well as various substitutions in positions 8, 15, or 28, and in some cases Agm in position 29, was evaluated in vivo. All five antagonists, administered at a 27-fold molar excess to rats, suppressed the GH-releasing effect of exogenous GH-RH(1-29)-NH2 by 64-75%. The inhibitory effects lasted for more than 15 min. The most potent analog, PhAc-[D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGH-RH(1-28)Agm (MZ-5-156), showed an in vivo potency 7-16 times higher than the early antagonist [Ac-Tyr1,D-Arg2]hGH-RH(1-29)-NH2, which was used as std., MZ-5-156 was capable of decreasing serum GH levels after i.v., i.p., or i.m. administration. In vitro, in the superfused rat pituitary cell system, MZ-5-156 induced a prolonged inhibition of GH release after continuous long-term administration and showed a potency more than 100 times greater than the std. antagonist. These results show that N-terminal acylation with phenylacetic acid of the sequence [D-Arg2,Phe(4-Cl)6,Nle27]hGH-RH(1-29)-NH2, contg. modification in positions 8, 15, 28, or 29, results in antagonists with high and protracted potency both in vivo and in vitro. In view of high antagonistic activity and prolonged duration of action, some of these antagonists of GH-RH may find clin. application for the treatment of IGF-dependent cancers.
IT **93942-91-7 190783-58-5 190783-59-6**
RL: PRP (Properties)
(growth hormone release inhibition in rats by antagonists of growth hormone-releasing hormone)

L4 ANSWER 20 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:294702 CAPLUS
DOCUMENT NUMBER: 127:76139
TITLE: Synthesis and in vitro evaluation of new potent antagonists of growth hormone-releasing hormone (GH-RH)
AUTHOR(S): Zarandi, Marta; Kovacs, Magdolna; Horvath, Judit E.; Toth, Katalin; Halmos, Gabor; Groot, Kate; Nagy, Attila; Kele, Zoltan; Schally, Andrew V.
CORPORATE SOURCE: Endocrine, Polypeptide and Cancer Institute and Department of Medicine, Tulane University School of Medicine, New Orleans, LA, 70146, USA
SOURCE: Peptides (Tarrytown, New York) (1997), 18(3), 423-430

CODEN: PPTDD5; ISSN: 0196-9781
PUBLISHER: Elsevier
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the search for more potent antagonists of hGH-RH, 20 new analogs were synthesized, purified and tested in vitro. All the analogs were based on the N-terminal sequence of 28 or 29 amino acid residues of hGH-RH, but contained D-Arg2 and Nle27 modifications. Most analogs had Phe(pCl)6 and Agm29 substituents. The effect of other substitutions such as Abu8 and/or Abu15 and Ala15 and various hydrophobic and hydrophilic D or L amino acids at position 8 were also investigated. All the peptides were acylated at the N-terminus in an attempt to increase the antagonistic activity. In the superfused rat pituitary cell system, most analogs inhibited more powerfully the GH release induced by GH-RH than the std. antagonist [Ac-Tyr1,D-Arg2]hGH-RH (1-29)-NH2. Some antagonists were long acting. Among the peptides synthesized, antagonist PhAc-[D-Arg2,Phe(pCl)6,Abu1,Nle27]hGH-RH(1-28)Agm (MZ-5-156) appeared to be the most potent and inhibited GH release in vitro 63-200 times more powerfully than the std. antagonist. MZ-5-156 and other antagonists showed high binding affinities to membrane receptors for GH-RH. Some of these hGH-RH antagonists could be further developed for possible oncol. applications.

IT **93942-91-7 190783-58-5 190783-59-6 190791-06-1 190791-07-2 190791-08-3 190975-92-9 190975-94-1**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); PROC (Process)
(growth hormone-releasing hormone antagonist in vitro evaluation in relation to structure and receptor binding)

L4 ANSWER 21 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1997:101825 CAPLUS
DOCUMENT NUMBER: 126:181577
TITLE: Suppression of growth hormone (GH) hypersecretion due to ectopic GH-releasing hormone (GHRH) by a selective GHRH antagonist
AUTHOR(S): Jaffe, Craig A.; DeMott-Frigerg, Roberta; Frohman, Lawrence A.; Barkan, Ariel L.
CORPORATE SOURCE: Department of Internal Medicine, Divisions of Endocrinology and Metabolism, Department of Verterans Affairs Medical Center, University of Michigan Medical Center, Ann Arbor, MI, 48109, USA
SOURCE: J. Clin. Endocrinol. Metab. (1997), 82(2), 634-637
CODEN: JCEMAZ; ISSN: 0021-972X
PUBLISHER: Endocrine Society
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The authors have recently demonstrated that a competitive antagonist of GHRH, (N-Ac-Tyr1,D-Arg2)GHRH-(1-29)NH2 (GHRH-Ant), eliminates nearly all nocturnal GH pulsatility in normal subjects, supporting the hypothesis that GH pulsatility is driven by GHRH. In this study, the authors compared the effects of every 12 h i.v. boluses of either GHRH-Ant or saline on 24-h GH profiles in a patient with acromegaly due to a metastatic GHRH-secreting carcinoid tumor. Bolus doses of GHRH-Ant (400 .mu.g/kg, i.v.) acutely suppressed GH concn. to 30-40% of the pretreatment baseline, and this effect lasted 3-4 h. Administration of GHRH (0.33 .mu.g/kg,i.v.) bolus resulted in a small rise in GH, and this effect was blocked by GHRH-Ant (400 .mu.g/kg). During saline treatment, the secretory patterns of both GH and ectopic GHRH were pulsatile; however, there was no correlation between changes in plasma GHRH and GH concns. This lack of correlation was probably due to the majority of circulating GHRH immunoreactivity consisting of nonbiol. active GHRH fragments. These data support the hypothesis that GH hypersecretion in the ectopic GHRH

syndrome requires GHRH receptor occupancy and validates the use of GHRH-Ant to probe the potential involvement of endogenous GHRH in patients with acromegaly due to pituitary somatotropinoma.

IT **93942-91-7**
RL: BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(suppression of growth hormone (GH) hypersecretion due to ectopic GH-releasing hormone (GHRH) by a selective GHRH antagonist)

L4 ANSWER 22 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:300265 CAPLUS
DOCUMENT NUMBER: 124:333537
TITLE: The inhibitory effects of growth hormone-releasing hormone (GHRH)-antagonist on GHRH, L-DOPA, and clonidine-induced GH secretion in normal subjects
AUTHOR(S): Hanew, Kunihiko; Tanaka, Aki; Utsumi, Atsushi; Sugawara, Akira; Abe, Keishi
CORPORATE SOURCE: Second Department Internal Medicine, Tohoku University School Medicine, Sendai, 980, Japan
SOURCE: J. Clin. Endocrinol. Metab. (1996), 81(5), 1952-1955
CODEN: JCEMAZ; ISSN: 0021-972X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The relative inhibitory potency of GHRH-Antagonist (GHRH-Ant) to GHRH(1-44)NH2 and mechanism of L-DOPA- or clonidine-induced GH release were studied in seven normal subjects using GHRH-Ant. One hundred micrograms of GHRH-Ant (i.v. for 75 min) did not inhibit plasma GH responses to bolus injection of 100 .mu.g and 10 .mu.g GHRH or simultaneous infusion of 5 .mu.g GHRH (i.v. for 75 min). However, 200 .mu.g GHRH-Ant (i.v. for 75 min) significantly inhibited GH release, which was induced by simultaneous infusion of 5 .mu.g GHRH. Although 100 .mu.g GHRH-Ant could not significantly inhibit L-DOPA-induced GH release, 200 .mu.g GHRH-Ant almost completely inhibited the response. Similarly, the same dose f GHRH-Ant markedly inhibited the GH-releasing activity of clonidine. It is concluded that the inhibitory potency of GHRH-Ant on GHRH(1-44)NH2 is relatively weak (about 1/60 in molar base), and that L-DOPA- or clonidine-induced GH release seems to be mediated by the release of hypothalamic GHRH.

IT **93942-91-7**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(the inhibitory effects of growth hormone-releasing hormone (GHRH)-antagonist on GHRH, L-DOPA, and clonidine-induced GH secretion in normal subjects)

L4 ANSWER 23 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1996:75144 CAPLUS
DOCUMENT NUMBER: 124:107207
TITLE: Plasma GH responses to human GHRH-antagonist in normal subjects
AUTHOR(S): Hanew, Kunihiko; Tanaka, Aki; Utsumi, Atsushi; Sugawara, Akira; Abe, Keishi
CORPORATE SOURCE: Second Dep. Internal Medicine, Tohoku Univ. School Medicine, Sendai, Japan
SOURCE: Eur. J. Endocrinol. (1996), 134(1), 67-72
CODEN: EJOEEP; ISSN: 0804-4643
DOCUMENT TYPE: Journal
LANGUAGE: English
AB The effect of GH-RH-antagonist {(N-Ac-Tyr1,D-Arg2)-GH-RH-(1-29)-NH2} on plasma GH morning and evening secretion was evaluated in 14 normal subjects (10 males, 4 females, aged 19-25 yr). Plasma GH was detd. using a high sensitivity IRMA kit (detection limit, 0.006 .mu.g/L). After i.v. infusion of GH-RH-antagonist (100 .mu.g/100 mL saline over 75 min) in the

morning, plasma GH remained const. during the 150 min post-infusion. In contrast, when GH-RH-antagonist was administered in the evening, plasma GH showed a clear and gradual decrease through the initial 90 min and returned to baseline levels at 150 min. Plasma GH values were also significantly lower from 75 min to 135 min when compared to physiol. fluctuations in plasma GH. Other anterior pituitary hormones remained unaffected by GH-RH-antagonist. In conclusion, the data suggest that evening basal GH secretion, but not morning GH secretion, is maintained by endogenous GH-RH.

IT **93942-91-7**
RL: BAC (Biological activity or effector, except adverse); BUU (Biological use, unclassified); BIOL (Biological study); USES (Uses)
(plasma growth hormone responses to human GH-RH antagonist in normal subjects)

L4 ANSWER 24 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:1002215 CAPLUS
DOCUMENT NUMBER: 124:21956
TITLE: Characterization of growth hormone-releasing hormone (GH-RH) binding to cloned porcine GH-RH receptor
AUTHOR(S): Hassan, Hazem A.; Hsiung, Hansen M.; Zhang, Xing-Yue; Smith, Dennis P.; Smiley, David L.; Heiman, Mark L.
CORPORATE SOURCE: Div. Endocrinology, Eli Lilly and Co., Indianapolis, IN, 46285, USA
SOURCE: Peptides (Tarrytown, N. Y.) (1995), 16(8), 1469-73
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB To study structure-activity relations of GH-RH, a competitive binding assay was developed using cloned porcine adenopituitary, GH-RH receptors expressed in human kidney 293 cells. Specific binding of [His1,125I-Tyr10,Nle27]hGH-RH-(1-32)-NH2 increased linearly with protein concn. (10-45 .mu.g protein/tube). Binding reached equil. after 90 min at 30.degree. and remained const. for at least 240 min. Binding was reversible to 1 class of high-affinity sites (Kd = 104 nM, Bmax = 3.9 pmol/mg protein). Binding was selective with a rank order of affinity (IC50) for porcine GH-RH (2.8 nM), rat GH-RH (3.1 nM), [N-Ac-Tyr1,D-Arg2]hGH-RH(3-29)-NH2 (3.9 nM), and [D-Thr7]GH-RH(1-29)-NH2 (189.7 nM), consistent with their binding to GH-RH receptor. Nonhydrolyzable guanine nucleotides inhibited binding. These data describe a selective and reliable method for a competitive GH-RH binding assay that for the first time utilizes rapid filtration to terminate the binding assay.

IT **93942-91-7**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(characterization of growth hormone-releasing hormone binding to cloned porcine GH-RH receptor)

L4 ANSWER 25 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:960194 CAPLUS
DOCUMENT NUMBER: 124:87800
TITLE: Preparation of analogs of human growth hormone releasing hormone hGH-RH(1-29)NH2 having antagonistic activity for hGH-RH
INVENTOR(S): Schally, Andrew V.; Zarandi, Marta
PATENT ASSIGNEE(S): Administrators of the Tulane Educational Fund, USA
SOURCE: PCT Int. Appl., 59 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

checked this document

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9516707	A1	19950622	WO 1994-US13714	19941128
W: AT, AU, BB, BG, BR, CA, CH, CZ, DE, DK, ES, FI, GB, HU, JP, KP, KR, LK, LU, MG, MN, MW, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SK, UA, US				
RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
US 5550212	A	19960827	US 1993-168810	19931217
AU 9513322	A1	19950703	AU 1995-13322	19941128
AU 695315	B2	19980813		
EP 734396	A1	19961002	EP 1995-904767	19941128
EP 734396	B1	20001108		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, NL, PT, SE				
ES 2152380	T3	20010201	ES 1995-904767	19941128
ZA 9409641	A	19950825	ZA 1994-9641	19941205

PRIORITY APPLN. INFO.: US 1993-168810 A 19931217
WO 1994-US13714 W 19941128

OTHER SOURCE(S): MARPAT 124:87800

AB Analogs of hGH-RH(1-29)NH2 having substitutions of various amino acids and acylated at the N-terminus X-R1-R2-R3-R4-R5-R6-Thr-R8-Ser-Tyr-R11-R12-Val-Leu-R15-Gln-Leu-Ser-R19-R20-R21-Leu-Leu-Gln-Asp-Ile-R27-R28-R29 [X = nil, H, Ac, ICH2CO, BrCH2CH2CO, CHO, Me2CHCH2CO, 1- or 2-naphthylacetyl, 1- or 2-naphthoyl, 1- or 2-naphthylpropionyl, anthraquinone-2-carbonyl; R1 = Tyr, His, Glu, glutaryl; R2 = D-Arg, D-Cit (citrulline), D-homoArg, D-Lys, D-Orn; R3 = Asp, Ala, Gly; R4 = Ala, Gly; R5 = Ile, Ala, Gly; R6 = Phe, Ala, Pro, 2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indole-3-carboxylic acid, 2-naphthylalanine, Phe(Y), in which Y = F, Cl, Br, NO2, Me, or OCH3; R8 is Asn, Ser, Val, Ile, Ala, Abu (.alpha.-aminobutyric acid), Nle, .alpha.-aminoisobutyric acid; R11 = Arg, D-Arg, Cit; R12 = Lys, D-Lys, Cit, Ala; R15 = Gly, Ala, Abu, Gln; R19 = Ala, Abu; R20 = Arg, D-Arg, Cit; R21 = Lys, D-Lys, Cit; R27 = Met, Nle, Abu; R28 = Ser, Asn, Asp, Abu; R29 = agmatine, Arg-NH2, Arg-OH, Cit-NH2, Cit-OH, homoArg-NH2, homoArg-OH; provided that when R1 is glutaryl, X is nil and When X is H, R15 is other than Gly] and pharmaceutically acceptable acid addn. salts thereof, which inhibit the release of hGH from the pituitary in mammals and exhibit prolonged antagonistic activity, are prepd. Thus, Nac-Tyr-D-Asp-Ala-Ile-Phe(p-Cl)-Thr-Asn-Ser-Tyr-Arg-Lys-Val-Leu-Abu-Gln-Leu-Ser-Ala-Arg-Lys-Leu-Leu-Gln-Asp-Ile-Nle-Ser-Agm-OH (I; Nac = 1-naphthylacetyl, Agm = agmatine) was prepd. by the solid phase method using Boc-Agm-SPA-aminomethyl resin (California Peptide Co.) and N-Boc-protected amino acids and acylation of the resin-bound peptide with 1-naphthylacetic anhydride on the NH2 group of Tyr. I in vitro at 30 nM inhibited the GH release from rat superfused pituitary system by 96, 98, and 48% 2, 4.5, and 6 h after the incubation, resp.

IT **160361-93-3P 160361-94-4P 160361-95-5P**
160499-35-4P 160499-40-1P 171047-63-5P
171047-64-6P 171047-66-8P 171047-67-9P
171047-69-1P
RL: BAC (Biological activity or effector, except adverse); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(prepn. of human growth hormone releasing hormone (hGH-RH) analogs as hGH-RH antagonists and inhibitors of hGH release from pituitary gland)

L4 ANSWER 26 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1995:259031 CAPLUS
DOCUMENT NUMBER: 122:96644
TITLE: Synthesis and biological activities of highly potent antagonists of growth hormone-releasing hormone
AUTHOR(S): Zarandi, M.; Horvath, J. E.; Halmos, G.; Pinski, J.; Nagy, A.; Groot, K.; Rekasi, Z.; Schally, A. V.
CORPORATE SOURCE: Vet. Affairs Med. Cent., Tulane Univ. Sch. Med., New

Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1994), 91(25), 12298-302
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In the search for antagonists of human growth hormone-releasing hormone (hGHRH) with high activity, 22 analogs were synthesized by solid-phase methods, purified, and tested biol. Within the N-terminal sequence of 28 or 29 amino acids of hGHRH, all the analogs contained D-Arg2,Phe(4-Cl)6 (para-chlorophenylalanine), Abu15 (.alpha.-aminobutyric acid), and Nle27 and most of them had Agm29 (agmatine) substituents. All the peptides, except one, were acylated at the N terminus with different hydrophobic acids-e.g., isobutyric acid (Ibu) or I-naphthylacetic acid (Nac) to study the effect of N-terminal acylation on the antagonistic activity. In the superfused rat pituitary cell system, all the analogs inhibited more powerfully the GHRH-induced growth hormone (GH) release than the std. GHRH antagonist [Ac-Tyr1,D-Arg2]hGHRH-(1-29)NH2. Antagonists [Ibu9,D-Arg2,Phe(4-Cl)6, Abu15,Nle27]hGHRH-(1-28)Agm (MZ-4-71), [Nac10,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-28)Agm (MZ-4-243), [Nac0,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-29)NH2 (MZ-4-169), [Nac0-His1,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-29)NH2 (MZ-4-181), and [Nac10,D-Arg2,Phe(4-Cl)6,Abu15,Nle27,Asp28]hGHRH-(1-28)Agm (MZ-4-209) inhibited GH release at 3.times.10-9 M. Among these peptides, MZ-4-243, MZ-4-169, and MZ-4-181 were also long acting in vitro. Antagonist MZ-4-243 inhibited GH release 100 times more powerfully than the std. antagonist and was the most potent in vitro among GHRH antagonists synthesized. Analogs with high inhibitory effects in vitro were also found to have high affinities to rat pituitary GHRH receptors. In expts. in vivo, antagonists [Ibu0,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-28)Agm (MZ-4-71), [Nac0,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-29)NH2 (MZ-4-169), and [Nac0-His1,D-Arg2,Phe(4-Cl)6,Abu15,Nle27]hGHRH-(1-29)NH2 (MZ-4-181) induced a significantly greater inhibition of GH release than the std. antagonist. In view of their high antagonistic activity and prolonged duration of action, some of these antagonists of GHRH may find clin. applications, including treatment of certain endocrine disorders and insulin-like growth factor I-dependent tumors.

IT **160361-93-3 160361-94-4 160361-95-5**
160499-35-4 160499-40-1
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(synthesis and biol. activities of highly potent antagonists of growth hormone-releasing hormone)

L4 ANSWER 27 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1994:293308 CAPLUS
DOCUMENT NUMBER: 120:293308
TITLE: Amino acid identification and sequence analysis of peptides by reaction mass spectrometry
AUTHOR(S): Yang, Houjun; Hu, Xiaoyu; Chen, Yaozu
CORPORATE SOURCE: State Key Lab. Appl. Org. Chem., Lanzhou Univ., Lanzhou, 730000, Peop. Rep. China
SOURCE: Chin. J. Chem. (1993), 11(6), 540-9
CODEN: CJOCEV
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fast-atom-bombardment mass spectrometry (FAB-MS) is used to distinguish N-terminal series ions from C-terminal series ions of a peptide by on-probe acetylation, and it provides valuable information about the sequence of an unknown peptide. The FAB mass spectra contain a no. of characteristic ions in the low-mass region in addn. to the sequence ions in the high-mass region. The ions below m/z 200 are characteristic of the amino acid compn. of the peptide, from which the amino acid compn. of the

peptide could be estd. Mixt. anal. also is discussed.
IT **121282-52-8**
RL: PRP (Properties)
(sequence of, detn. of, by fast-atom-bombardment mass spectrometry)

L4 ANSWER 28 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:420652 CAPLUS
DOCUMENT NUMBER: 119:20652
TITLE: Position 2 and position 2/Ala15-substituted analogs of bovine growth hormone-releasing factor (bGRF) with enhanced metabolic stability and improved in vivo bioactivity
AUTHOR(S): Kubiak, Teresa M.; Friedman, Alan R.; Martin, Roger A.; Ichhpurani, Avneet K.; Alaniz, Glenn R.; Claflin, William H.; Goodwin, Martha C.; Cleary, Diane L.; Kelly, Colleen R.; et al.
CORPORATE SOURCE: Upjohn Co., Kalamazoo, MI, 49001, USA
SOURCE: J. Med. Chem. (1993), 36(7), 888-97
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To prep. GRF analogs with high activity in vivo, a strategy was undertaken to stabilize the peptide to dipeptidylpeptidase IV (DPP-IV), a protease found in plasma which inactivates native human and bovine GRF by cleavage of the Ala2-Asp3 bond. Replacement of the Ala2 residue with Ser, Thr, or Gly in [Leu27]bGRF(1-29)NH2 resulted in peptides greatly stabilized against proteolysis in plasma, but having low inherent GH-releasing activity when tested in bovine pituitary cell cultures. Replacement of Gly15 with Ala15 was marginally effective in improving the in vitro bioactivity of this group of peptides. When tested for GH-hormone release in steers, however, the Thr2,Ala15 analog was four times more potent than bGRF(1-44)NH2. Eleven addnl. analogs from the [X2,Ala15,Leu27]bGRF(1-29)NH2 series were synthesized and evaluated for metabolic stability in bovine plasma and for GH releasing activity in steers in vivo and in rat pituitary cells in vitro. Two compds., [Val2,Ala15,Leu27]bGRF(1-29)NH2 and [Ile2,Ala15,Leu27]bGRF(1-29)NH2, had increased GH-releasing activity in steers over that of [Thr2,Ala15,Leu27]bGRF(1-29)NH2 and over a previously reported super-potent analog, [desNH2Tyr1,D-Ala2,Ala15]hGRF(1-29)NH2.
IT **148298-15-1**
RL: BIOL (Biological study)
(growth hormone-releasing activity and biol. stability of, structure in relation to)

L4 ANSWER 29 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1993:401079 CAPLUS
DOCUMENT NUMBER: 119:1079
TITLE: A method for evaluation of activity of antagonistic analogs of growth hormone-releasing hormone in a superfusion system
AUTHOR(S): Rekasi, Zoltan; Schally, Andrew V.
CORPORATE SOURCE: Med. Sch., Tulane Univ., New Orleans, LA, 70146, USA
SOURCE: Proc. Natl. Acad. Sci. U. S. A. (1993), 90(6), 2146-9
CODEN: PNASA6; ISSN: 0027-8424
DOCUMENT TYPE: Journal
LANGUAGE: English
AB To evaluate the endocrine effect of GH-releasing hormone (GHRH) antagonists, a sensitive dynamic in vitro system was developed. The concn. causing 50% inhibition (IC50) of the std. GHRH antagonist human [N-Ac-Tyr1, D-Arg2]GHRH-(1-29)-NH2 is 4.5 .times. 10-8M in the dispersed pituitary cell superfusion system. This value is 11-fold less than that measured in earlier static pituitary cell cultures. This reliable dynamic system is simple, fast, and inexpensive and not only makes it possible to

obtain quant. data on the inhibitory capacity of the antagonists but also provides information about the intrinsic GHRH activity of the analog. The dynamic interactins of the GHRH antagonist, the GHRH receptors, and GH release can also be evaluated by this superfusion system. The pulsatile GH release induced by 10-9M human GHRH-(1-29)-NH2 was inhibited by 2 modes of application, preincubation and simultaneous administration of the GHRH antagonist (10-9-10-6M). The redn. in GHRH-stimulated GH response was more pronounced when the cells were preincubated with the antagonist prior to GHRH infusion than for simultaneous application. The inhibitory effect of the antagonist was dose-dependent, temporary, and of the competitive type. GH release induced by nonspecific stimulus (100 mM KCl) was not influenced by the GHRH antagonist. This sensitive dynamic in vitro system appears to be a suitable method for screening the biol. activity of various GHRH antagonists and eliminates the drawbacks of static pituitary cell culture.

IT **93942-91-7**
RL: ANST (Analytical study)
(somatoliberin antagonistic activity of, method for evaluation of, in superfusion system of anterior pituitary cells)

L4 ANSWER 30 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1992:76528 CAPLUS
DOCUMENT NUMBER: 116:76528
TITLE: Human growth hormone-releasing hormone analogs with much improved in vitro growth hormone-releasing potencies in rat pituitary cells
AUTHOR(S): Coy, David H.; Hocart, Simon J.; Murphy, William A.
CORPORATE SOURCE: Med. Cent., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Eur. J. Pharmacol. (1991), 204(2), 179-85
CODEN: EJPHAZ; ISSN: 0014-2999
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Enhancement of the amphiphilic .alpha.-helical properties of the central and C-terminal regions of growth hormone-releasing hormone (GRH) by substitution with helix-favoring amino acids, particularly Ala, can result in improvements in GH-releasing potencies using monolayer cultures of rat pituitary cells, a system which reflects analog receptor affinity rather than effects of structural modifications on pharmacokinetic properties. For instance, helix-enhanced [Ala15]GRH-(1-29)NH2 was 5-fold more potent than [Gly15]GRH-(1-29)NH2 in this assay. The extent and importance of .alpha.-helical character further towards the N-terminus is less clear since Chou-Fasman probability calcns. indicate also the possibility of .beta.-bend formation in the 6-10 region. However, replacement of Asn8 with Ala resulted in a 4-fold improvement in potency; when this was combined with Ala15 to give [Ala8,15]GRH-(1-29)NH2 a 15-fold increase in potency was achieved; combination of D-Ala2, Ala8, and Ala15 gave a 27-fold increase, indicating that the effects of all of these modifications were additive. Computer anal. furthermore revealed that substitution of Ala for Ser in position 9 should also increase .alpha.-helix probability from 0.93 to 1.05. [D-Ala2,Ala8,9,15]GRH-(1-29]NH2 was 49-fold more potent than GRH itself, making it by far the most potent analog thus far reported in an in vitro assay system. The Ala8 and Ala9 substitutions were also effective in improving the inhibitory potency of a GRH receptor antagonist, [D-Ala2,Leu27]GRH-(1-29)NH2. [D-Arg2,Ala8,15]GRH-(1-29)NH, and [D-Arg2,Ala8,9,15]GRH-(1-29)NH2 displayed IC50 values of 5.9 .times. 10-8 and 1.7 .times. 10-8M, resp., against GRH-stimulated GH release compared with an IC50 of 2.2 .times. 10-7M for the unmodified control analog, and are thus commensurate with corresponding agonist analog potency improvements.

IT **138659-23-1 138659-25-3 138659-26-4**
RL: BIOL (Biological study)
(growth hormone release inhibition by, structure in relation to)

L4 ANSWER 31 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1990:229806 CAPLUS
DOCUMENT NUMBER: 112:229806
TITLE: Synthetic analogs of growth hormone-releasing factor with antagonistic activity in vitro
AUTHOR(S): Sato, Kazuki; Hotta, Mari; Kageyama, Jingo; Hu, Hsiaoyu; Dong, Minghui; Ling, Nicholas
CORPORATE SOURCE: Dep. Mol. Endocrinol., Whittier Inst. Diabetes Endocrinol., La Jolla, CA, 92037, USA
SOURCE: Biochem. Biophys. Res. Commun. (1990), 167(1), 360-6
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Analogs of human and rat growth hormone-releasing factor (hGRF and rGRF), related to [D-Arg2]hGRF(1-29)NH2, were synthesized by solid phase methodol. Their capacity to inhibit growth hormone secretion stimulated by hGRF(1-44)NH2 was tested on rat anterior pituitary cells in monolayer culture. Among the analogs of hGRF, [D-Arg2,29,Arg30]hGRF(1-30)NH2 showed the highest antagonistic potency of 3.64 relative to [D-Arg2]hGRF(1-29)NH2 = 1. However, the most potent analog synthesized thus far was [N-Ac-His1,D-Arg2,Ala15]rGRF(1-29)NH2, which showed a relative potency of 27.7.
IT **93942-91-7 93942-95-1 121282-52-8 121282-56-2 121282-57-3 121396-16-5 121396-17-6 121448-26-8 126883-97-4 126883-98-5 127119-77-1**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(growth hormone-releasing factor agonist and antagonist activity of)

L4 ANSWER 32 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:471103 CAPLUS
DOCUMENT NUMBER: 111:71103
TITLE: Growth hormone-releasing factor analogs with potent antagonist activity
AUTHOR(S): Ling, Nicholas; Sato, Kazuki; Hotta, Mari; Chiang, Teh Chang; Hu, Hsiau Yu; Dong, Ming Hui
CORPORATE SOURCE: Lab. Neuroendocrinol., Salk Int., La Jolla, CA, 92037, USA
SOURCE: Pept.: Chem. Biol., Proc. Am. Pept. Symp. 10th (1988), Meeting Date 1987, 484-6. Editor(s): Marshall, Garland R. ESCOM Sci. Pub.: Leiden, Neth.
CODEN: 56MDA6
DOCUMENT TYPE: Conference
LANGUAGE: English
AB A series of human somatoliberin (1-29) amide [hGRF(1-29)NH2] analogs were prepd. and examd. for antagonist activity along with their capacity to release growth hormone (GH) from rat anterior pituitary cells in vitro. Substitution of a D-arginine group in the 2nd position resulted in antagonist activity whereas compds. with an L-arginine in the 2nd position were inactive and those with D-arginine in the 4th position were only weakly active. N-terminal acetylation decreased GRF receptor binding affinity but suppression of GH secretion was improved. Increasing the basicity at the N-terminal region gave a weaker agonists. The analogs [D-Arg2,29Tyr30]- and [D-Arg2,29,Arg30]-hGRF(1-30)NH2 showed improved affinity and max. suppression. The rat GRF (rGRF) analog [D-Arg2,Ala15]rGRF(1-29)NH2 was more potent an antagonist than [D-Arg2]hGRF(1-29)NH2. Evidently, modification of the N-terminal residue is required to suppress agonist activity, whereas modification at position 15 is needed to increase affinity for the receptor.
IT **93942-91-7 93942-95-1 121282-52-8 121282-58-4 121396-17-6**
RL: BAC (Biological activity or effector, except adverse); BIOL

(Biological study)
(growth hormone-releasing factor agonist and antagonist activity of)

L4 ANSWER 33 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:433758 CAPLUS
DOCUMENT NUMBER: 111:33758
TITLE: Structure-activity relations of growth hormone-releasing factor (GRF)
AUTHOR(S): Sato, Kazuki; Hotta, Mari; Kageyama, Jingo; Chiang, Teh Chang; Hu, Hsiao Yu; Dong, Ming Hui; Ling, Nicholas
CORPORATE SOURCE: Salk Inst., La Jolla, CA, 92037, USA
SOURCE: Pept. Chem. (1989), Volume Date 1988, 26th, 85-90
CODEN: PECHDP; ISSN: 0388-3698
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cyclic analogs of human growth hormone-releasing factor (hGRF) (1-29)NH2, known to retain most of the biol activity of the native mol., were synthesized and intrinsic activities and antagonist potencies compared by using a rat anterior pituitary cell culture. The hGRF(1-29)NH2 analogs contained cyclic modifications as follows: Cys2 linked to Cys15, Cys3 to Cys14, Cys4 to Cys13, Cys5 to Cys15, Cys2 to Cys13 and Cys5 to Cys14. All the analogs were weak agonists. Analogs (28) were prepd. with a corresponding D-amino acid at each position of hGRF(1-29)NH2, except for glycine at position 15. Analogs with D-Ile5, D-Phe6, D-Thr7, and D-Val13 were much less potent than hGRF(1-29)NH2, suggesting that the specific conformation of these positions is important for the binding of the analogs to the hGRF receptor. Since [D-Arg7]hGRF(1-29)NH2 had low intrinsic activity and some antagonistic activity, a series of similarly modified analogs of rat GRF were prepd. The N-terminally acetylated analog ([N-Ac-Tyr1,D-Arg2]hGRF(1-29)NH2 was a more effective antagonist them [D-Arg2]hGRF(1-29)NH2, because it showed lower intrinsic activity than the [D-Arg2]peptide. The [D-Arg2,D-Asn8,Ala15] analog had higher antagonistic potency than [D-Arg2]hGRF(1-29)NH2; however, it also had higher intrinsic activity. [D-Arg2,29,Arg30]hGRF(1-30)NH2 was the most potent antagonist in the hGRF series. In the rat series [N-Ac-His1,D-Arg2,Ala15]hGRF(1-29)NH2 was the most potent antagonist. These compds. were prepd. studied on part of a search for specific antagonists of hGRF for clin. and research uses.
IT **93942-91-7 93942-95-1 121282-52-8 121282-56-2 121282-57-3 121282-58-4 121396-16-5 121396-17-6 121396-19-8 121448-26-8**
RL: PRP (Properties)
(structure-somatoliberin activity relation of)

L4 ANSWER 34 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:166384 CAPLUS
DOCUMENT NUMBER: 110:166384
TITLE: Blockade of growth hormone-releasing factor (GRF) activity in the pituitary and hypothalamus of the conscious rat with a peptidic GRF antagonist
AUTHOR(S): Lumpkin, Michael D.; McDonald, John K.
CORPORATE SOURCE: Sch. Med., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Endocrinology (Baltimore) (1989), 124(3), 1522-31
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Microinjection of synthetic growth hormone-releasing factor (GRF) into the cerebroventricles or hypothalamus of the rat produces a no. of neural effects, including the suppression of growth hormone (GH) secretion, possibly representing a neg. ultrashort loop autoregulation of GRF and/or

stimulation of somatostatin neurosecretion. To demonstrate that such neuromodulation acts physiol. through endogenous GRF activity, the peptidic GRF antagonist (N-Ac-Tyr1, D-Arg2)GRF-(1-29)-NH2 was used to block the action of GRF on its presumed receptors in the hypothalamus. First, to establish the efficacy of the antagonist to block GRF receptors in the anterior pituitary, the antagonist was injected i.v. at doses of 2,20, and 50 .mu.g into conscious male rats fitted with jugular cannulae. Sequential blood sampling every 15 min for 6 h between 1000-1600 h showed that 50 .mu.g antagonist, i.v., suppressed the 2 periods of spontaneous release of RIAable GH in controls in the morning and afternoon. A dose of 20 .mu.g, i.v., lowered mean plasma GH between 1400-1500 h, whereas the 2-.mu.g dose was without effect. The GRF antagonist was then microinjected into the third ventricle (3V) of conscious male rats at doses of 0.5 and 8.0 ng in 2 .mu.L sterile saline. The 8.0-ng dose of 3V antagonist elicited a 3-fold increase in the morning peak of GH (nanograms per mL): 3V antagonist, 159.0; 3V control, 51.0. The 0.5-ng dose was without effect. Finally, pretreatment with the GRF antagonist 3V (10 ng), followed 15 min later by 10 ng rat GRF administered 3V, completely blocked the GRF-induced suppression of pulsatile GH release obsd. earlier. Both the systemic and central effects of the antagonist were specific to the control of GH, since prolactin concns. were unaltered. These results (1) demonstrated the ability of a peptidic GRF antagonist to specifically suppress pulsatile GH release after its systemic administration, presumably by acting on pituitary GRF receptors, and (2) support the notion that GRF receptors are also present in the hypothalamus and are available for the physiol. mediation of GRF-induced inhibition of GH release by a central mechanism.

IT **93942-91-7**
RL: BIOL (Biological study)
(growth hormone-releasing factor receptors of hypothalamus and pituitary gland binding of, growth hormone secretion in relation to)

L4 ANSWER 35 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1989:148244 CAPLUS
DOCUMENT NUMBER: 110:148244
TITLE: Inhibition of pulsatile growth hormone (GH) secretion and somatic growth in immature rats with a synthetic GH-releasing factor antagonist
AUTHOR(S): Lumpkin, Michael D.; Mulroney, Susan E.; Haramati, Aviad
CORPORATE SOURCE: Sch. Med., Georgetown Univ., Washington, DC, 20007, USA
SOURCE: Endocrinology (Baltimore) (1989), 124(3), 1154-9
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Indwelling Silastic catheters were placed into the jugular veins of immature male rats (120-140 g) at 29 days of age. After a recovery period of 48 h, beginning at 1000 h, 100-400 .mu.g (N-Ac-Tyr1,D-Arg2)growth hormone-releasing factor-(1-29)-NH2 (GRF antagonist)/kg or its vehicle (controls) were injected i.v. immediately after withdrawing an initial blood sample from conscious undisturbed animals. Subsequent samples were obtained every 20 min until 1520 h. Red blood cells were resuspended in a restorative vol. of saline and reinjected after each blood sample. Both doses of antagonist prevented the 2 major periods of episodic growth hormone (GH) release obsd. in controls. For example, mean plasma GH (nanograms per mL) at 1120 h was 9.0 in antagonist-treated rats and 37.1 in controls. Mean plasma GH at 1340 h was 10.8 in antagonist-treated rats and 38.8 in controls. Injection of 400 .mu.g/kg of the structurally related VIP antagonist (N-Ac-Tyr1,D-Phe2)GRF-(1-29)-NH2, i.v. failed to suppress spontaneous GH release. GRF antagonist (100 .mu.g/kg) was next administered twice daily i.v. for 4 days to 31-day-old rats in metabolic cages. This treatment essentially arrested the normal rapid body wt.

gain, significantly suppressed increases in body and tail lengths, and reduced increases in heart and kidney wts. Food intake and fecal output were unchanged by antagonist treatment and, therefore, did not contribute to the obsd. effects. Apparently, a no. of tissues and organs are stimulated by the pulsatile secretion of GH and a peptidic GRF receptor antagonist is useful in blocking episodic GH release in immature animals. As a consequence, this specific antagonist is effective in suppressing numerous aspects of somatic growth.

IT **93942-91-7**
RL: BIOL (Biological study)
(growth and somatotropin secretion inhibition by)

L4 ANSWER 36 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1988:448562 CAPLUS
DOCUMENT NUMBER: 109:48562
TITLE: Synthesis and in vitro bioactivity of human growth hormone-releasing factor analogs substituted with a single D-amino acid
AUTHOR(S): Sato, Kazuki; Hotta, Mari; Kageyama, Jingo; Chiang, Teh Chang; Hu, Hsiao Yu; Dong, Ming Hui; Ling, Nicholas
CORPORATE SOURCE: Lab. Neuroendocrinol., Salk Inst., La Jolla, CA, 92037, USA
SOURCE: Biochem. Biophys. Res. Commun. (1987), 149(2), 531-7
CODEN: BBRCA9; ISSN: 0006-291X
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Fifty-four analogs of human growth hormone-releasing factor (hGRF) substituted with a single D-amino acid were synthesized by solid phase methodol. Their capacity to release growth hormone was tested on rat anterior pituitary cells in monolayer culture. Among the series of 28 analogs which had the amino acid at each position of hGRF (1-29)NH2, except glycine at position 15, substituted by the corresponding D-isomer, [D-Ala2]-, [D-Asp3]-, [D-Asn8]-, [D-Tyr10]-, [D-Asp25]-, [D-Met27]-, [D-Ser28]-, and [D-Arg29]hGRF(1-29)NH2 were as potent as hGRF(1-29)NH2, while [D-Ile5]-, [D-Phe6]-, [D-Thr7]-, and [D-Val13]hGRF(1-29)NH2 showed quite low potencies. Effects of substitution with other D-amino acids in positions 2, 3, 8, 9, 10 and 11 were also studied. In most cases, the resulting analogs showed decreased potency, but still retained high intrinsic activity. Only [D-Arg2]hGRF(1-29)NH2 showed very low intrinsic activity and some antagonistic property.

IT **93942-91-7P 93942-95-1P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and growth hormone release by, structure in relation to)

L4 ANSWER 37 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:576483 CAPLUS
DOCUMENT NUMBER: 107:176483
TITLE: (N,N'-dialkylguanidino)amino acyl GRF analogs
INVENTOR(S): Nestor, John J.
PATENT ASSIGNEE(S): Syntex (U.S.A.), Inc., USA
SOURCE: U.S., 11 pp. Cont.-in-part of U.S. Ser. No. 605,346, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 4659693	A	19870421	US 1985-707007	19850228
PRIORITY APPLN. INFO.:			US 1984-605346	19840430

AB The title compds. [I; R1 = H, D- or L-H-Tyr, N-methyltyrosyl, His, R2, excluding D- or L-Ala and D- or L-Leu; R2 = D- or L-Ala, D- or L-Leu, Q, where n = 1-5; S1 = alkyl, etc.; S2 = H; S1C(:NS2) = 5H-imidazol-2-yl, etc,; R3 = Asp, Asn, Glu; R4 = Ala, Gly; R8 = Asn, Ser; R11 = D-Tyr, Phe; R12 = Lys, Arg; R13 = Ile, Val; R15 = Gly, D-Ala; R18 = Ser, Tyr; R24 = Gln, His; R25 = Glu, Asp; R27 = D- or L-Nle, D-or L-Ile, D- or L-Leu, D- or L-Met, D- or L-Val; R28 = Asn, Ser, D-Ala; R34 = Arg, Ser, Ala; R38 = Gln, Arg, Ser; R39 = Arg, Gly; R40 = Ala, Ser, Arg, bond; R41 = Arg, Phe, Lys, bond; R42 = Val, Phe, Ala, Gln, Gly, Ile, Leu, Lys, Pro, bond; R43 = Asn, Arg, bond; R44 = Leu, bond], were prepd. [D-HArg(Et2)2]1-29(NH2)-hGRF was prepd. via solid-phase synthesis using a benzhydrylaminopolystyrene-1% divinylbenzene resin.

IT **110781-88-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as growth hormone releasing factor analog)

L4 ANSWER 38 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1987:691 CAPLUS
DOCUMENT NUMBER: 106:691
TITLE: Comparative structural requirements of thirty GRF analogs for interaction with GRF and VIP receptors and coupling to adenylate cyclase in rat adenopituitary, liver and pancreas
AUTHOR(S): Robberecht, Patrick; Waelbroeck, Magali; Coy, David; De Neef, Philippe; Camus, Jean Claude; Christophe, Jean
CORPORATE SOURCE: Med. Sch., Univ. Libre Bruxelles, Brussels, Belg.
SOURCE: Peptides (Fayetteville, N. Y.) (1986), 7(Suppl. 1), 53-9
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The ability of (1-29)-human growth hormone-releasing factor-NH2 [(1-29)-GRF-NH2] [86168-78-7] and 30 analogs to stimulate adenylate cyclase [9012-42-4] activity was investigated in membranes from adenopituitary, liver, and pancreas of rat. In adenopituitary membranes, GRF and GRF analogs interacted with specific GRF receptors, whereas in liver and pancreatic membranes, they interacted with VIP [37221-79-7] receptors. The C-terminal moiety of GRF was responsible for GRF receptor recognition, since the hybrid analog [(1-9)-(His1,D-Ala2)-GRF]-(10-28)-VIP [105605-65-0] stimulated pituitary adenylate cyclase through the occupancy of VIP receptors only. When GRF of VIP receptors were occupied by GRF analogs, the N-terminal part of the ligand appeared crit. for adenylate cyclase activation. This was established by testing 30 GRF analogs mono-, bi-, or tri-substituted in positions 1-10. Major observations included: the characterization of (1-29)-(N-Ac-Tryl,D-Arg2)-GRF-NH2 [**93942-91-7**] as an antagonist of GRF-stimulated pituitary adenylate cyclase; the discovery of (1-29)-(N-Ac-Tyr1,D-Phe2)-GRF-NH2 [93965-89-0], (1-29)-(His1,D-Ala2,D-Ser3,NLeu27)-GRF-NH2 [105581-54-2], and (1-29)-(His1,D-Ala2,D-Thr7,NLeu27)-GRF-NH2 [105568-06-7] as specific antagonists of VIP receptors in rat pancreatic membranes; the importance of the free NH2 function of amino acid residue 1 for pancreatic adenylate cyclase activation; and the decreased efficiency of iodinated (1-29)-(Try1)-GRF-NH2 as opposed to the noniodinated form, in all systems tested.

IT **93942-91-7**
RL: BIOL (Biological study)
(adenylate cyclase of rat stimulation by, of human, receptors of liver and pancreas and pituitary gland in relation to)

L4 ANSWER 39 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1986:565181 CAPLUS
DOCUMENT NUMBER: 105:165181

TITLE: Strategies in the design of synthetic agonists and antagonists of growth hormone releasing factor
AUTHOR(S): Coy, David H.; Murphy, William A.; Lance, Valentine A.; Heiman, Mark L.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: Peptides (Fayetteville, N. Y.) (1986), 7(Suppl. 1), 49-52
CODEN: PPTDD5; ISSN: 0196-9781
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Analog studies on the sequence-related 1-12 region of growth hormone-releasing factor (1-29) amide [GRF(1-29)NH2] [86168-78-7] carried out. Replacement of each of the 1st 11 amino acids by its D-isomer in turn gave a total of 5 analogs exhibiting increases in potency. Other analogs contg. multiple D-amino acid replacements were also examd. and potent, for instance: D-Tyr-1,D-Ala-2 [104670-92-0], 2630; His-1,D-Ala-2 [104670-93-1], 3440; Ac-His-1,D-Ala-2 [93942-90-6], 1574; D-Ala-2,Nle-27 [101366-31-8], 1840; D-Ala-2,D-Asn-8,Nle-27 [101383-49-7], 1580; D-Ala-2,D-Asp-3,D-Asn-8,Nle-27 [104670-94-2], 2000; D-Asp-3,D-Asn-8,Nle-27 [101366-32-9], 3810 (GRF(1-29) = 100%). These results with D-isomers may reflect the presence of reverse turns (.beta.-bends) in this region of GRF. Indeed, the qual. predictive method of Chou and Fasman supports this theory and indicates reverse turns in the 1-5 and 6-10 sequences. In introducing even more rigidity into the N-terminal region via disulfide bond formation between positions normally contg. arom. amino acids, none of the bridged peptides displayed biol. activity which suggests that chain folding does not produce any proximity among N-terminal residues. Since position 2 was extremely sensitive to both conformational and side-chain alterations, this observation was extended to analogs contg. sarcosine and proline, both of which were also inactive on growth hormone (GH) [9002-72-6] release at the doses tested. Previously, 2 position 2 analogs, Ac-D-Tyr-1,D-Arg-2 [**104670-95-3**]- and [Ac-Tyr-1,D-Phe-2]-GRF(1-29)NH2 [93965-89-0] were found to be competitive antagonists of GRF adenylate cyclase activity in various tissues but were not able to block the in vivo or in vitro GH-releasing activity of GRF. Likewise, none of the new position 2 peptides were able to block the GH-releasing activity of GRF indicating that their loss of biol. activity is caused by reduced receptor affinities.

IT **104670-95-3**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(growth hormone releasing activity of, structure in relation to)

L4 ANSWER 40 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:606774 CAPLUS
DOCUMENT NUMBER: 103:206774
TITLE: Structural requirements for the activation of rat anterior pituitary adenylate cyclase by growth hormone-releasing factor (GRF): discovery of (N-Ac-Tyr1, D-Arg2)-GRF(1-29)-NH2 as a GRF antagonist on membranes
AUTHOR(S): Robberecht, Patrick; Coy, David H.; Waelbroeck, Magali; Heiman, Mark L.; De Neef, Philippe; Camus, Jean Claude; Christophe, Jean
CORPORATE SOURCE: Med. Sch., Univ. Libre Bruxelles, Brussels, B-1000, Belg.
SOURCE: Endocrinology (Baltimore) (1985), 117(5), 1759-64
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The efficacy and potency of 14 growth hormone-releasing factor (GRF) analogs, substituted in position 1-7, on adenylate cyclase [9012-42-4] activation in crude homogenates from rat anterior pituitary were related

to those of human pancreatic GRF(1-29)-amide [86168-78-7] and VIP [37221-79-7]. Among several D-amino acid substitutions, that in position 2 was the only 1 to yield a super-agonist [with a Kact (concn. required for half-maximal adenylate cyclase activation) 2-fold lower than that of GRF(1-29)-NH2]. By contrast, D-isomer substitution in position 1 and 3 was without effect and D-isomer substitution in position 4, 6, or 7 decreased the affinity of the analog. The N-acetylated analog of GRF was as potent and active as the parent peptide, and the identity of the amino acid in position 2 of [N-Ac-Tyr1]-GRF(1-29)-NH2 was detd. for enzyme activation, with D-Phe2 and D-Trp2 derivs. acting as partial agonists and the [N-Ac-Tyr1,D-Arg2) analog being an efficient competitive antagonist of GRF(1-29)-NH2. With use of this antagonist, it was possible to demonstrate that GRP and VIP receptors represent distinct entities in the rat anterior pituitary.

IT **93942-91-7**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(adenylate cyclase of anterior pituitary response to)

L4 ANSWER 41 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:448326 CAPLUS
DOCUMENT NUMBER: 103:48326
TITLE: Interaction of growth hormone-releasing factor (GRF) and 14 GRF analogs with vasoactive intestinal peptide (VIP) receptors of rat pancreas. Discovery of (N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 as a VIP antagonist
AUTHOR(S): Waelbroeck, Magali; Robberecht, Patrick; Coy, David H.; Camus, Jean Claude; De Neef, Philippe; Christophe, Jean
CORPORATE SOURCE: Med. Sch., Univ. Libre Bruxelles, Brussels, B-1000, Belg.
SOURCE: Endocrinology (Baltimore) (1985), 116(6), 2643-9
CODEN: ENDOAO; ISSN: 0013-7227
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Adenylate cyclase [9012-42-4] stimulation by human pancreatic growth hormone-releasing factor (GRF) [83930-13-6] and 14 GRF analogs (modified in the N-terminal part) was compared to the capacity of the same peptides to inhibit 125I- labeled VIP [37221-79-7] binding in rat pancreatic plasma membranes. These peptides interfered with VIP receptors as they inhibited 125I-VIP binding, and probably acted through VIP-preferring receptors as one of these peptides [(N-Ac-Tyr1,D-Phe2)-GRF(1-29)-NH2 [93965-89-0]] selectively inhibited both VIP- and GRF-stimulated adenylate cyclase activities. Alterations in positions 6 and 7 (but not in positions 1-4) markedly reduced the affinity of the resulting GRF analog [based on Kact (concn. exerting half-maximal stimulation) values]. The intrinsic activity exerted by GRF analogs on adenylate cyclase was reduced by acetylation of the free NH2 group and by the replacement of Asp3, Ala4, Phe6, and Thr7 by the corresponding D-isomer. The presence of pCl-Phe6 and Trp6 also depressed this parameter. Substitution in GRF (or its N-acetylated deriv.) by D-Phe2, D-Arg2, and D-Ala4 again reduced the intrinsic activity, whereas substitution of the natural L-amino acid residue by D-Ala2 and Phe4 gave superagonists.

IT **93942-91-7**
RL: BIOL (Biological study)
(adenylate cyclase stimulation by, in pancreas membrane, VIP receptor binding in relation to)

L4 ANSWER 42 OF 42 CAPLUS COPYRIGHT 2002 ACS
ACCESSION NUMBER: 1985:56275 CAPLUS
DOCUMENT NUMBER: 102:56275
TITLE: Structure-activity studies on the N-terminal region of growth hormone releasing factor

Searched by Barb O'Bryen, STIC 308-4291

AUTHOR(S): Coy, David H.; Murphy, William A.; Sueiras-Diaz, Javier; Coy, Esther J.; Lance, Valentine A.
CORPORATE SOURCE: Sch. Med., Tulane Univ., New Orleans, LA, 70112, USA
SOURCE: J. Med. Chem. (1985), 28(2), 181-5
CODEN: JMCMAR; ISSN: 0022-2623
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The effect of replacement of some L-amino acids with D-amino acids in the pancreatic growth hormone-releasing factor (1-29)-amide [GRF(1-29)] [86168-78-7] on its activity was investigated. The effect of side-chain chem. on the position 2-D-amino acid and substituents on the phenylalanine ring in position 6 were also examd. The analogs were synthesized by the solid-phase method on benzhydrylamine resin, purified by medium-pressure reverse-phase liq. chromatog., and tested in male rats. [4-D-Alanine]-GRF [94061-36-6] showed a slightly higher activity than GRF, [5-D-isoleucine]-GRF [94062-18-7], an analog further along the peptide chain from the N-terminus, showed loss of activity, whereas [8-D-asparagine]-GRF [94061-38-8] was twice as active as GRF. Structure-activity relations are discussed.

IT **93942-95-1**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(growth hormone-releasing activity of)

IT **93942-91-7P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and growth hormone-releasing activity of)

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